PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE

AFILAT 5 (Film coated tablets)

AFILAT 20 (Film coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AFILAT 5: Each film coated tablet contains 5 mg tadalafil.

Contains lactose monohydrate: 60 mg.

AFILAT 20: Each film coated tablet contains 20 mg tadalafil.

Contains lactose monohydrate: 240 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

AFILAT 5: Yellow, 8.00 mm x 4.90 mm, almond shaped, film coated tablet, debossed with 'T5' on one side and plain on other side.

AFILAT 20: Yellow, 12.25 mm x 7.45 mm, almond shaped, film coated tablet, debossed with 'T20' on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

In adult men:

AFILAT 5: The recommended dose is 5 mg taken once a day at approximately the same time of day.

AFILAT 20: The recommended maximum dose of AFILAT 20 is 20 mg taken prior to anticipated sexual activity and without regard to food.

It 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

In men with impaired renal function

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

Method of administration

Oral route.

4.3 Contraindications

AFILAT is contraindicated in:

- Patients with hypersensitivity to tadalafil or to any of the excipients (see section 6.1);
- Patients who are using any form of organic nitrate (see section 4.6);
- Patients with severe hepatic insufficiency (Child-Pugh Class C) (see section 4.4);
- Patients with previous experience of partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes (see section 4.4). AFILAT 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).
- Patients with previous experience of unilateral or bilateral decrease or loss of hearing with or without associated vestibular symptoms (see section 4.4).

4.4 Special warnings and precautions for use

Prior to initiating any treatment for erectile dysfunction, medical practitioners should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. 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.

Tadalafil has vasodilatory properties resulting in mild and transient decreases in blood pressure. Patients with underlying cardiovascular disease may be adversely affected by such vasodilatory effects.

For patients with pre-existing cardiovascular disease sexual activity carries a potential cardiac risk. AFILAT should not be used in patients with cardiac disease for whom sexual activity is not advised.

The use of AFILAT in the following group of patients with cardiovascular disease is not recommended:

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

Simultaneous administration of AFILAT in patients who are taking alpha-[1] blockers, such as doxazosin (4-8 mg daily), should be done with caution as this may lead to symptomatic hypotension in some patients.

No symptomatic hypotension is observed with simultaneous administration of tamsulosin, an -[1A] blocker, with a single dose of tadalafil.

AFILAT, 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). Priapism has been reported with tadalafil. 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.

Visual defects and cases of Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) have been reported in connection with the intake of AFILAT and other PDE5 inhibitors. It is not

possible to determine whether NAION is related directly to the use of PDE5 inhibitors or other factors.

As this may be relevant for all patients exposed to tadalafil, the

patient should be advised that in case of sudden visual defect, to stop taking AFILAT and consult a medical practitioner immediately. Medical practitioners should also discuss with patients that individuals who have already experienced NAION are at increased risk of NAION and should not use AFILAT or other PDE5 inhibitors again.

Cases of sudden hearing loss, which may be accompanied by tinnitus and dizziness, have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history) patients should be advised to stop taking AFILAT and seek prompt medical attention in the event of sudden decrease or loss of hearing.

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

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of AFILAT is not recommended in patients with severe renal impairment. The taking of AFILAT in patients with moderate renal failure (creatinine clearance = 31 to 50 mL/min) is safe, however less well tolerated in terms of back pain than in patients with mild renal failure (creatinine clearance = 51 to 80 mL /min) and healthy patients.

AFILAT is contraindicated in patients with severe hepatic insufficiency (Child-Pugh Class C) (see section 4.3). Safety and efficacy of once-a-day administration in patients with hepatic insufficiency have not been established.

Caution should be exercised when prescribing AFILAT 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.

Paediatric population

There is no relevant use of AFILAT in the paediatric population with regard to the treatment of erectile dysfunction.

Excipients

AFILAT contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P450

CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 is not inhibited or induced by AFILAT.

AFILAT is principally metabolised by CYP3A4. Ketoconazole (400 mg daily), a selective inhibitor of CYP3A4 increased tadalafil 20 mg exposure (AUC) by 312 % and C_{max} by 22 %. AFILAT 10 mg exposure (AUC) is increased by ketoconazole (200 mg daily) by 107 % and C_{max} by 15 % relative to the AUC and C_{max} values for tadalafil alone.

Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, CYP2C9, CYP2C19 and CYP2D6, increased tadalafil exposure (AUC) by 124 % with no change in C_{max}. Other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors such as erythromycin, clarithromycin, and itraconazole and grapefruit juice, would likely increase tadalafil plasma concentrations.

A selective CYP3A4 inducer, rifampicin (rifampicin, 600 mg daily), reduced tadalafil AUC by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for tadalafil alone. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of tadalafil.

The reduced exposure of tadalafil with the co-administration of rifampicin can be anticipated to decrease the efficacy of once-a-day-dosed AFILAT.

Nitrates

Tadalafil may increase the hypotensive effects of nitrates. The use of AFILAT in patients who are also taking any form of organic nitrate is contra-indicated.

Anti-hypertensives and alpha-adrenergic blockers

The co-administration of alpha-[1]-adrenergic blocker 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 in a significant manner. This effect can last at least twelve hours and some patients may experience dizziness.

Although AFILAT may not have an effect on blood pressure changes due to tamsulosin, caution should be exercised when using tadalafil in patients treated with tamsulosin or any alpha-blockers.

AFILAT may increase the blood pressure lowering effects of antihypertensive medicines. In patients whose hypertension is not well controlled taking multiple antihypertensive medicines may cause greater reductions in blood pressure.

CYP1A2 substrates (e.g., theophylline)

Tadalafil had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a non-selective phosphodiesterase inhibitor.

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.

Antacids

Administration of tadalafil with antacids (magnesium hydroxide/aluminium hydroxide) reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

Alcohol

Tadalafil does not affect alcohol concentrations and alcohol does not affect tadalafil concentrations.

H_2-antagonists:

An increase in gastric pH resulting from administration of nizatidine, an H2-antagonist, had no significant effect on tadalafil pharmacokinetics.

CYP2C9 substrates (e.g., warfarin)

Tadalafil does not affect changes in prothrombin time induced by warfarin. Tadalafil has no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate).

Aspirin

Tadalafil does not potentiate the increase in bleeding time caused by acetylsalicylic acid.

4.6 Fertility, pregnancy and lactation

AFILAT is not indicated for use by women.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of AFILAT during pregnancy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. AFILAT should not be used during breast feeding

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1).

4.7 Effects on ability to drive and use machines

AFILAT may have effects on the ability to drive and use machines. Undesirable effects may occur (e.g., allergic reaction, dizziness or blurred vision), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Immune system disorders	Less frequent	Hypersensitivity reactions, angioedema
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, stroke (including haemorrhagic events), syncope, transient ischaemic attacks, migraine, seizures, transient amnesia
Eye disorders	Less frequent	Blurred vision, sensations described as eye pain
	Unknown	Visual field defect, swelling of eyelids, conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion
Ear and labyrinth disorders	Less frequent	Tinnitus, sudden hearing loss
Cardiac disorders	Less frequent	Tachycardia, palpitations, myocardial infarction,

		unstable angina pectoris, ventricular dysrhythmia
Vascular disorders	Frequent	Flushing
	Less frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion
	Less frequent	Dyspnoea, epistaxis
Gastrointestinal system disorders	Frequent	Dyspepsia
	Less frequent	Abdominal pain, vomiting, nausea, gastro-oesophageal reflux
Skin and subcutaneous tissue disorders	Less frequent	Rash, urticaria, Stevens-Johnson syndrome, exfoliative dermatitis, hyperhidrosis (sweating)
Musculoskeletal and connective tissue disorders	Less frequent	Back pain, myalgia
Reproductive system and breast disorders	Less frequent	Prolonged erections, priapism, penile haemorrhage, haematospermia

b. 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

Multiple daily doses up to 100 mg and single doses of up to 500 mg have been given to healthy subjects. Adverse events are similar to those seen at lower doses.

Treatment

In cases of overdose, treatment is symptomatic and supportive 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: Medicines used in erectile dysfunction

ATC code: G04BE08

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 results in increased levels of cGMP in the corpus cavernosum. This results in penile erection during sexual stimulation caused by increased penile blood flow resulting from the relaxation of penile arteries and the smooth muscle of the corpus cavernosum. Tadalafil has no effect in the absence of sexual stimulation.

Tadalafil is a potent and selective inhibitor of PDE5. PDE5 is an enzyme found in several tissues, like corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung and cerebellum. Tadalafil is far more selective for PDE5 than for PDE isoenzymes which are widely distributed in heart, brain tissue, blood vessels, liver, and other organs, which mediate numerous processes.

This selectivity for PDE5 over PDE3 is clinically important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil has low selectivity for PDE6, an enzyme, which is distributed in the retinal cells and is responsible for phototransduction. Tadalafil shows no impairment of colour discrimination (blue/green), a finding which is to be expected since tadalafil has a low affinity for PDE6 compared to PDE5. In addition, no effects have been documented on visual acuity, electroretinograms, intraocular pressure, or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (<0,1%).
Tadalafil is also >9 000-fold more potent for PDE5 than for PDE 8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11.

Non-arteritic anterior ischaemic optic neuropathy (NAION) is a vascular event that is associated with decreased vision including permanent loss of vision. There are reports of NAION in temporal association with the use of all PDE5 inhibitors, including tadalafil. Currently it is not possible to confirm whether NAION is directly related to the use of PDE5 inhibitors or other factors.

Effect on blood pressure and heart rate – Tadalafil administered to healthy subjects has shown no clinically relevant effects compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1,6/0,8 mm Hg, respectively), in standing

systolic and diastolic blood pressure compared to placebo (mean maximal decrease of 0,2/4,6 mm Hg, respectively), and no significant change in heart rate. Larger effects have been documented in individuals receiving concomitant nitrates. Tadalafil should not be used in combination with nitrates.

Effects on erectile function – Studies in general populations have shown that 81 % of patients reported that tadalafil improved their erections. In primary efficacy studies, 75 % of intercourse attempts were reported to be successful in tadalafil-treated patients.

Tadalafil 5 mg significantly improves erectile function over the 24-hour period between the doses.

Tadalafil 20 mg demonstrates statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse, as early as 16 minutes following dosing

Paediatric population

There is no relevant use of AFILAT in the paediatric population with regard to the treatment of erectile dysfunction.

5.2 Pharmacokinetic properties

Absorption

Tadalafil is well absorbed after oral administration; peak plasma concentrations usually attained within 0.5–6 hours. Mean maximum observed plasma concentration (C_{max}) is achieved on average 2 hours after dosing.

Food does not appear to affect the rate and extent of absorption. Tadalafil may be taken with no regard to food.

The time of dosing appears to not have any clinically relevant effect on the rate and extent of absorption.

Distribution

At therapeutic concentrations plasma protein binding is at approximately 94 %. Less than 0,0005 % of the administered dose could be found in the semen of healthy subjects. Tadalafil is distributed in tissues. The mean volume of distribution is approximately 63 L.

Biotransformation

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

Elimination

The mean half-life in healthy subjects is 17,5 hours. Tadalafil is predominantly excreted as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose). The mean oral clearance for tadalafil is 2,5 l/h.

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. The result is a 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. The effect of age does not warrant a dose adjustment since it is not clinically significant.

Renal insufficiency

Tadalafil exposure (AUC) approximately doubles in subjects with mild (creatinine clearance 51 to 80 mL) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment and in subjects with end-stage renal disease on dialysis. C_{max} was 41 % higher in haemodialysis patients than that observed in healthy subjects.

Hepatic insufficiency

No dose adjustment is required in patients with mild and moderate hepatic impairment (Child-Pugh Class A and B). No data is 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

Lactose monohydrate

Low substituted hydroxypropyl cellulose

Hydroxy propyl cellulose

Sodium lauryl sulphate

Cellulose, microcrystalline

Magnesium stearate

Instacoat Aqua III A03G30218 (Hypromellose, lactose monohydrate, triacetin, talc, titanium dioxide (E171), yellow iron oxide (E 172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

AFILAT 5: PVC/PVDC/PE/Alu blister packs containing 28 tablets.

AFILAT 20: PVC/PVDC/PE/Alu blister packs containing 2 or 4 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 HOLDERS OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

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2031

8 REGISTRATION NUMBER(S)

AFILAT 5: 56/7.1.5/0476.474

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9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

03 October 2023

10 DATE OF REVISION OF THE TEXT

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