PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIALIS, 20 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg tadalafil.

Each film-coated tablet contains 233 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The tablets are yellow film-coated and almond shaped, marked 'C 20' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adult men

The recommended maximum dose of CIALIS is 20 mg taken prior to anticipated sexual activity and without regard to food. CIALIS can be taken up to 36 hours and as early as 16 minutes prior to sexual

activity. Patients may initiate sexual activity at various time points relative to dosing in order to determine their own optimal window of responsiveness.

The maximum recommended dosing frequency is one tablet once per day.

Method of administration

CIALIS is for oral use.

4.3 Contraindications

A known hypersensitivity to the active substance, tadalafil, or to any of the excipients listed in section 6.1.

Administration of CIALIS to patients who are using any form of organic nitrate

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Patients with severe hepatic insufficiency (Child-Pugh Class C).

The following groups of patients with cardiovascular disease were excluded in clinical trials, and the use of tadalafil is therefore contraindicated:

- Patients with myocardial infarction within the last 90 days.
- Patients with unstable angina 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 with a stroke within the last 6 months.

CIALIS is contraindicated in patients who have loss of vision in one 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).

The combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is contraindicated because it may lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with CIALIS

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment before pharmacological treatment is considered.

Medical practitioners should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. 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.

CIALIS has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing CIALIS, medical practitioners should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

Cardiovascular

Sexual activity carries a potential cardiac risk for patients with pre-existing cardiovascular disease. CIALIS should not be used in men with cardiac disease for whom sexual activity is inadvisable.

Caution should be exercised when prescribing CIALIS to patients who are taking α-1 blockers, such as prazosin and doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients (see section 4.5).

When tadalafil, as contained in CIALIS, was co-administered to healthy subjects taking doxazosin (4 to 8 mg daily), an alpha-1-adrenergic blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin.

Vision

There are postmarketing reports of NAION in temporal association with the use of all PDE5 inhibitors, including CIALIS. NAION is a cause of decreased vision including permanent loss of vision. An increased risk of acute NAION has been suggested from analyses of observational data in men with ED within 1 to 4 days of episodic PDE5 inhibitor (such as CIALIS) use. Medical practitioners should advise patients to stop use of CIALIS and seek medical attention in the event of a sudden loss of vision. Medical practitioners should also inform patients that individuals who have already experienced NAION should not use CIALIS or other PDE5 inhibitors again (see section 4.3).

Decreased or sudden hearing loss

Medical practitioners should advise their patients to stop taking CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see section 4.8).

Hepatic impairment

There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). It is therefore contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Renal impairment

In a clinical pharmacology study, administration of CIALIS to patients with moderate renal failure (creatinine clearance = 31 to 50 ml/min) was less well tolerated in terms of back pain than in patients with mild renal failure (creatinine clearance = 51 to 80 ml/min) and healthy subjects.

Priapism and anatomical deformation of the penis

Priapism has been reported with CIALIS. 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.

CIALIS should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing CIALIS 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).

CIALIS and other treatments for erectile dysfunction

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

CIALIS contains lactose monohydrate

Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take CIALIS.

CIALIS contains sodium

CIALIS contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effects of other substances on CIALIS

Cytochrome P450 inhibitors

CIALIS is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased CIALIS 20 mg single-dose exposure (AUC) by 312 % and C_{max} by 22 % and ketoconazole (200 mg daily) increased CIALIS 10 mg single-dose exposure (AUC) by 107 % and C_{max} by 15 % relative to the AUC and C_{max} values for CIALIS alone (see section 4.4).

Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increased CIALIS single-dose exposure (AUC) by 124 % with no change in C_{max}. Although specific interactions have not been studied, other HIV protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors such as erythromycin, clarithromycin, itraconazole and grapefruit, should be co-administered with caution as they would likely increase CIALIS exposure (see section 4.4).

Cytochrome P450 inducers

A selective CYP3A4 inducer, rifampicin (rifampicin 600 mg daily), reduced CIALIS single-dose exposure (AUC) by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for CIALIS alone. It can be expected that concomitant administration of other CYP3A4 inducers will also decrease plasma concentrations of CIALIS. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Antacids

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

H_2-antagonists

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

Effects of CIALIS on other medicinal products

Nitrates

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

Based on the results of a clinical study in which 150 subjects receiving daily doses of tadalafil 20 mg for 7 days and 0,4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Thus, in a patient prescribed any dose of CIALIS (2,5 mg to 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Antihypertensive medicines (including calcium channel blockers)

When tadalafil (5 mg daily dose and 20 mg as a single dose), as contained in CIALIS, was co-administered to healthy subjects taking doxazosin (4 and 8 mg daily), an alpha[1]-adrenergic blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide

diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers) is, in general, minor and not likely to be clinically relevant. Analysis of phase clinical trial data showed no difference in 3 adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat

Preclinical studies showed an 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 tadalafil, is contraindicated (see section 4.3).

5- alpha reductase inhibitors

In a clinical trial that compared tadalafil 5 mg co-administered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However,

as a formal drug-drug 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.

CYP1A2 substrates (e.g. theophylline)

CIALIS 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

CIALIS did not affect alcohol concentrations and alcohol did not affect CIALIS concentrations. At high doses of alcohol (0,7 g/kg), the addition of CIALIS did not induce statistically significant mean blood pressure decreases; however, postural dizziness and orthostatic hypotension were observed. When CIALIS 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 medicinal products

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

CYP2CP substrates (e.g. R-warfarin)

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

Aspirin

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

4.6 Fertility, pregnancy and lactation

CIALIS is not indicated for use by women.

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 and 5.3).

4.8 Effects on ability to drive and use machines

CIALIS has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to CIALIS, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of CIALIS. The adverse reactions reported were transient, and generally mild or moderate.

Tabulated summary of adverse reactions

Frequency convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000) and not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity reactions	Angiodema[1]
Vascular Disorders		Flushing	Hypotension[3], Hypertension	
Gastrointestinal Disorders		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Musculoskeletal, Connective tissue and Bone Disorders		Back pain, Myalgia, Pain in extremity		
Nervous System Disorders	Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2],	

			Transient amnesia	
Respiratory, Thoracic and Mediastinal Disorders		Nasal congestion	Dyspnoea, Epistaxis	
Eye Disorders			Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			Tinnitus	Sudden hearing loss
Skin and subcutaneous tissue disorders			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis

				(sweating)
Renal and urinary disorders			Haematuria	
Reproductive system and breast disorders			Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			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) Postmarketing 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 reactions

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

Data in patients over 65 years of age receiving tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. 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. In clinical trials with tadalafil 5mg taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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. Alternatively, report suspected adverse events to the company at ade_za@lilly.com.

4.9 Overdose

In cases of overdose, standard symptomatic and supportive measures should be adopted as required. Haemodialysis contributes negligibly to CIALIS elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction

ATC Code: G04BE08

Mechanism of action

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. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, PDE4 and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, leucocytes, skeletal muscle and other organs. Tadalafil is >10 000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels.

This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. 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 > 9 000-fold more potent for PDE5 than for PDE 8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

Studies on blood pressure and heart rate

Tadalafil administered to healthy subjects produced no significant difference 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.

Studies on vision

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with

the low affinity of tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure, or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (< 0,1 %).

Studies on spermatogenesis

Three studies were conducted in men to assess the potential effect on spermatogenesis of CIALIS 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

Studies on erectile function

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21 to 86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81 % of patients reported that CIALIS improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking CIALIS (86 %, 83 %, and 72 % for mild, moderate, and severe, respectively, as compared to 45 %, 42 %, and 19 % with placebo). In the primary efficacy studies, 75 % of intercourse attempts were successful in CIALIS treated patients as compared to 32 % with placebo.

In a 12-week study performed in 186 patients (142 tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with tadalafil 10 or 20 mg (flexible- 1 dose, on demand) of 48 % as compared to 17 % with placebo.

5.2 Pharmacokinetic properties

Absorption

After oral administration the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food. Thus, CIALIS 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, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0,0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP)3A4 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 oral clearance for tadalafil is 2,5 l/h and the mean half-life is 17,5 hours in healthy subjects. Tadalafil is excreted predominantly 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).

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.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

Pharmacokinetics in 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 insufficiency

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 haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency

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. There is limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). It is therefore contraindicated in patients with severe hepatic insufficiency (see section 4.3). There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment.

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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3,7 to 18,6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

lactose monohydrate,

croscarmellose sodium,

hydroxypropylcellulose,

microcrystalline cellulose,

sodium laurylsulphate,

magnesium stearate.

Film-coating

lactose monohydrate,

hypromellose,

triacetin,

titanium dioxide (E171),

iron oxide (E172),

talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in original package.

Keep out of reach of children.

6.5 Nature and contents of container

CIALIS is available as aluminium/PVC or aluminium/PVC/PE/PCTFE blister strips packed in cartons of 2, 4 or 8 tablets.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

First Floor, Golden Oak House, Ballyoaks Office Park

35 Ballyclare Drive

Bryanston, 2191

Johannesburg

Gauteng, South Africa

8. REGISTRATION NUMBER

36/7.1.5/0384

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2003

10. DATE OF REVISION OF THE TEXT

05 May 2023

Registration Details for Botswana: Schedule 2	
Cialis	Reg. No.: BOT0300576
Registration Details for Namibia: Schedule NS2	
Cialis	Reg. No.: 04/7.1.5/1467