PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

CIALIS 5 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CIALIS 5 film-coated tablet contains 5 mg tadalafil.

Contains lactose.

Each CIALIS 5 mg film-coated tablet contains 121 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

CIALIS 5 are film-coated, yellow, almond-shaped tablets debossed with identification code “C 5”.

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.

CIALIS is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia in adult males.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

Posology

Erectile dysfunction in adult men

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

Benign prostatic hyperplasia

The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day.

Special populations

Elderly men

Dose adjustments are not required in elderly patients.

Men with renal impairment

Dosage adjustments are not required in patients with mild or moderate renal impairment. Once-a-day dosing of tadalafil, both for the treatment of erectile dysfunction or benign prostatic hyperplasia, is not recommended in patients with severe renal impairment.

Men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

CIALIS should not be used in children.

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).

Previous experience of partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes.

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 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.

The combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is contraindicated because it may lead to symptomatic hypotension (see section 4.4).

The following groups of patients with cardiovascular disease were excluded in clinical trials, and safety in these patients is unknown. Therefore, use of CIALIS is contraindicated in the following groups of patients:

- 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.

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.

Prior to initiating treatment with CIALIS for benign prostatic hyperplasia (BPH), patients should be examined to rule out the presence of carcinoma of the prostrate.

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, physicians 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. When tadalafil, as contained in CIALIS, was co-administered to healthy patients 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

Nonarteritic anterior ischaemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. There are postmarketing reports of NAION in temporal association with the use of all PDE5 inhibitors, including CIALIS. 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 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).

Renal and hepatic impairment

Due to increased CIALIS exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of CIALIS is not recommended in patients with severe renal 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). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If CIALIS is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing medical practitioner.

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 PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

CIALIS contains lactose monohydrate

Patients with rare hereditary problems 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 other medicines and other forms of interaction

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

Effects of other substances on tadalafil

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, ~~and~~ itraconazole and grapefruit juice should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil (see section 4.4). Consequently the incidence of the adverse reactions listed in section 4.8 might be increased.

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 patients 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 - 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)

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. Therefore this combination is not recommended (see section 4.4).

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

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 16 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 -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in 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 coadministered 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 co44 administered with 5-ARIs.

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.

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.

CYP1A2 substrates (e.g. theophylline)

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

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.

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).

4.7 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 using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking CIALIS for the treatment of erectile dysfunction or benign prostatic hyperplasia 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. The majority of headaches reported with CIALIS once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo controlled clinical trials (comprising a total of 8022 patients on CIALIS and 4422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

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).

	Frequency of occurrence			
System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**
Immune system disorders			Hypersensitivity reactions	Angioedema[2]
Vascular disorders		Flushing	Hypotension[3], Hypertension	
Gastrointestinal disorders		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Skin and subcutaneous tissue disorders			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)

Musculoskeletal, connective tissue and bone disorders		Back pain Myalgia, Pain in extramity		
Renal and urinary disorders			Haematuria	
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, Nonarteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders			Tinnitus	Sudden hearing loss
Cardiac disorders[1]			Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular dysrhythmia[2]
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 1 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 5 mg 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Alternatively, report suspected adverse events to the company at ade_za@lilly.com.

4.9 Overdose

In cases of overdose, standard 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 treatment of erectile dysfunction in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The resulting vascular relaxation increases blood perfusion which may be the mechanism by which symptoms of benign prostatic hyperplasia are reduced. These vascular effects may be complemented by inhibition of bladder afferent nerve activity and smooth muscle relaxation of the prostate and bladder.

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, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, 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 > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

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 (mean maximal decrease of 0,2/4,6 mm Hg, respectively), and no significant change in heart rate.

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. Across all clinical studies, reports of changes in colour vision were rare (< 0,1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis 1 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.

Erectile dysfunction

For CIALIS on demand, three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated 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 compared to placebo as early as 16 minutes following dosing.

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 dose, on demand) of 48 % as compared to 17 % with placebo.

For once-a-day evaluation of tadalafil at doses of 2,5 mg and 5 mg and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21 to 82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67 % on CIALIS 5 mg, 50 % on CIALIS 2,5 mg as compared to 31 and 37 % with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46 % on CIALIS 5 mg and 2,5 mg, respectively, as compared to 28 % with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naïve to PDE5 inhibitors were randomized to CIALIS 5 mg once a day vs. placebo. The mean per-

subject proportion of successful sexual intercourse attempts was 68 % for CIALIS patients compared to 52 % for patients on placebo.

Benign prostatic hyperplasia

CIALIS was studied in 4 clinical studies of 12 weeks duration enrolling over 1500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with CIALIS 5 mg in the four studies were -4,8, -5,6, -6,1 and -6,3 compared to -2,2, -3,6, -3,8 and -4,2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0,4 mg as an active comparator, the improvement in total international prostate symptom score with CIALIS 5 mg, tamsulosin and placebo were -6,3, -5,7 and -4,2 respectively.

One of these studies assessed improvements in erectile dysfunction and signs and symptoms of benign prostatic hyperplasia in patients with both conditions. The improvements in the erectile function domain of the international index of erectile function and the total international prostate symptom score in this study were 6,5 and -6,1 with CIALIS 5 mg compared to 1,8 and -3,8 with placebo, respectively. The mean per-subject proportion of successful sexual intercourse attempts was 71,9 % with CIALIS 5 mg compared to 48,3 % with placebo.

The maintenance of the effect was evaluated in an open-label extension to one of the studies, which showed that the improvement in total international prostate symptom score seen at 12 weeks was maintained for up to 1 additional year of treatment with CIALIS 5 mg.

5.2 Pharmacokinetic properties

Absorption

Tadalafil is readily absorbed after oral administration and 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 patients.

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.

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 clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. 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 when a dose of 10 mg is administered. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If CIALIS

is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

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 1000 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 – 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,

hydroxypropyl cellulose,

microcrystalline cellulose,

sodium laurylsulphate,

magnesium stearate.

Film-coating

lactose monohydrate,

hypromellose,

triacetin,

titanium dioxide (E171),

iron oxide yellow (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 5 is available in aluminium/PVC/PE/PCTFE blisters, with a clear plastic web film, in cartons of 14 or 28 tablets. Each blister contains 14 tablets and there are either one or two blisters per carton.

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. 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

Telephone: +27 11 510 9300

8. REGISTRATION NUMBER

CIALIS 5: 41/7.1.5/0644

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration of CIALIS 5: 14 August 2009

10. DATE OF REVISION OF THE TEXT

20 November 2025