

CIALIS

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 10mg film-coated tablets.

CIALIS 20mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10mg tablet contains 10mg tadalafil.

Each 20mg tablet contains 20mg tadalafil.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The 10mg tablets are light yellow and almond shaped, marked 'C 10' on one side.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

In order for CIALIS to be effective, sexual stimulation is required.

CIALIS is not indicated for use by women.

4.2 Posology and method of administration

For oral use.

Use in adult men

The recommended dose is 10mg taken prior to anticipated sexual activity and without regard to food. In those patients in whom tadalafil 10mg does not produce an adequate effect, 20mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dosing frequency is once per day.

Continuous daily use of the medication is strongly discouraged because the long-term safety after prolonged daily dosing has not been established and also because the effect of tadalafil usually lasts for longer than one day. See sections 4.4 Special warnings and special precautions for use last paragraph and 5.1 Pharmacodynamic properties.

Use in elderly men

Dosage adjustments are not required in elderly patients.

Use in men with impaired renal function

Dosage adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment 10 mg is the maximum recommended dose. (See section 5.2 Pharmacokinetic properties).

Use in men with impaired hepatic function

The recommended dose of CIALIS is 10mg taken prior to anticipated sexual activity and without regard to food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10mg of tadalafil to patients with hepatic impairment. (See sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Use in men with diabetes

Dosage adjustments are not required in diabetic patients.

Use in children and adolescents

CIALIS should not be used in individuals below 18 years of age.

4.3 Contraindications

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 Interaction with other medicinal products and other forms of interaction).

Agents for the treatment of erectile dysfunction, including CIALIS, should not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included 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 arrhythmias, hypotension (<90/50mmHg), or uncontrolled hypertension.
- patients with a stroke within the last 6 months.

CIALIS should not be used in patients with hypersensitivity to tadalafil or to any of the excipients.

4.4 Special warnings and special precautions for use

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

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1 Pharmacodynamic properties) and as such potentiate the hypotensive effect of nitrates (see section 4.3 Contraindications).

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to CIALIS, to sexual activity, or to a combination of these or other factors.

There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

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.

Agents for the treatment of erectile dysfunction, including CIALIS, 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).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if CIALIS is effective in patients with spinal cord injuries and patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

CIALIS should not be administered to patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

In patients who are taking alpha(1) blockers, such as doxazosin, concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5 interaction with other medicinal products and other forms of interaction).

Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers.

PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor.

Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.

- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.

- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.

- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

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 drugs are combined (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

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.

In dogs given tadalafil daily for 6 to 12 months at doses of 25mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans at a 20mg single dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. Results from two 6-month studies in volunteers suggest that this effect is unlikely in humans (see section 5.1 Pharmacodynamic properties). The effects of longer-term daily dosing have not been established. Therefore, daily use of the medication is strongly discouraged.

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Physicians should also discuss with patients the

increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 and/or 20 mg tadalafil, as indicated below. With regard to those interaction studies where only the 10mg tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other medicinal products on tadalafil

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10-mg) exposure (AUC) 2-fold and C_{max} by 15%, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20-mg) exposure (AUC) 4-fold and C_{max} by 22%. Ritonavir, a protease inhibitor (200 mg dose given twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20-mg) exposure (AUC) 2-fold with no change in C_{max}. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice, should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil. Consequently the incidence of the undesirable effects listed in section 4.8 might be increased.

The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. There is thus the potential of drug interactions mediated by inhibition of transporters.

A CYP3A4 inducer, rifampicin, reduced tadalafil AUC by 88%, relative to the AUC values for tadalafil alone (10mg dose). It can be expected that concomitant administration of other CYP3A4 inducers, such as phenobarbital, phenytoin and carbamazepine, will also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

In clinical studies, tadalafil (10mg and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of CIALIS to patients who are using any form of organic nitrate is contra-indicated (see section 4.3 Contraindications). 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 CIALIS, 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.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolised by CYP450 isoforms. Studies have confirmed that tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

Tadalafil (10mg and 20mg) 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.

Tadalafil (10mg and 20mg) did not potentiate the increase in bleeding time caused by acetylsalicylic acid.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive agents was examined. Major classes of antihypertensive agents were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluzide), 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 (10mg, except for studies with angiotensin II receptor blockers and amlodipine in which a 20mg 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 medications, tadalafil 20mg may induce a blood pressure decrease, which (with the exception of alpha blockers – see below-) 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 medications. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medications.

In subjects receiving concomitant tadalafil (20 mg) and doxazosin (8 mg daily), an alpha (1)-adrenergic receptor blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. This effect was still present at 12 hours postdose and had generally disappeared at 24 hours. The number of subjects with potentially clinically significant standing-blood-pressure decreases was greater for the combination. Some subjects experienced dizziness but no cases of syncope were reported. Lower doses of doxazosin have not been studied. In a single study in 18 healthy volunteers, tadalafil (10 and 20 mg) had no clinically significant effect on blood pressure changes due to tamsulosin, a selective alpha (1A)-adrenergic receptor blocking agent. It is not known how this extrapolates to other alpha (1A)-adrenergic receptor blocking agents.

Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10 or 20 mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximize the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol). Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40% alcohol [vodka] in an 80-kg male) but 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. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

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.

When tadalafil 10mg 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 medications.

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

CIALIS is not indicated for use by women. There are no studies of tadalafil in pregnant women.

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1000mg/kg/day.

4.7 Effects on ability to drive and use machines

CIALIS is expected to have no or negligible influence on the ability to drive and/or use machines. No specific studies have been performed to evaluate a potential effect. 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

The most commonly reported adverse reactions are headache and dyspepsia, see tables below.

Table 1			
<i>Very common adverse reactions (>1/10)</i>			
System Organ Class	Adverse reaction	CIALIS 10-20 mg (%) N=724	Placebo (%) N=379
Nervous System	Headache	14.5	5.5
Gastrointestinal	Dyspepsia	12.3	1.8

Table 2			
<i>Common adverse reactions (>1/100, <1/10)</i>			
System Organ Class	Adverse reaction	CIALIS 10-20 mg (%) N=724	Placebo (%) N=379
Nervous System	Dizziness	2.3	1.8
Vascular	Flushing	4.1	1.6
Respiratory, thoracic, and mediastinal	Nasal Congestion	4.3	3.2
Musculoskeletal and connective tissue	Back pain	6.5	4.2
	Myalgia	5.7	1.8

Swelling of eyelids, sensations described as eye pain and conjunctival hyperaemia are uncommon adverse reactions.

The adverse events reported with tadalafil were transient, and generally mild or moderate.

Adverse event data are limited in patients over 75 years of age.

In postmarketing surveillance, adverse events/reactions that have been reported very rarely in patients taking tadalafil include:

Ophthalmologic: visual field defect, retinal vein occlusion

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking.

It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Body as a whole: hypersensitivity reactions including rash, urticaria, facial oedema, Stevens-Johnson syndrome, and exfoliative dermatitis.

Cardiovascular and cerebrovascular: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had preexisting cardiovascular risk factors (See section 4.4 Special warnings and precautions for use).

Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension, and syncope.

Skin and subcutaneous tissues: hyperhidrosis (sweating).

Gastrointestinal: abdominal pain and gastro-oesophageal reflux.

Urogenital: priapism and prolonged erection.

4.9 Overdose

Single doses of up to 500mg have been given to healthy subjects, and multiple daily doses up to 100mg 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

Pharmacotherapeutic group: Drugs used in erectile dysfunction (ATC Code G04B E).

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.

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.

Three clinical studies were conducted in 1054 patients in an at-home setting to define the period of responsiveness to CIALIS. CIALIS 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.

CIALIS administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8mmHg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6mmHg, 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%).

Two studies were conducted in men to assess the potential effect of CIALIS 10mg and 20mg administered daily for 6 months on spermatogenesis. The results of these studies demonstrate no difference from placebo with respect to the proportion of men showing a 50% or greater decrease in sperm concentration. In addition, in comparison with placebo, there were no adverse effects observed with respect to mean change in sperm count, sperm morphology, or sperm motility at either dose. However, in the study of 10mg CIALIS taken daily for 6 months, results showed a decrease in mean sperm concentration relative to placebo. This effect was not seen in the study where the higher dose, 20mg, CIALIS was taken daily for 6 months. In addition, there was no effect on mean concentrations of

testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20mg of CIALIS compared to placebo. The effects of longer-term daily dosing have not been established. See also Sections 4.4 Special warnings and special precautions for use and 5.3 Preclinical safety data.

Tadalafil at doses of 2 to 100mg has been evaluated in 16 clinical studies involving 3,250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 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.

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 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 20mg, 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 (5-20 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 10mg is administered.

There is limited clinical data on the safety of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10mg 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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1,000mg/kg/day. In a rat pre- and postnatal development study, the no observed effect dose was 30mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20mg 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 25mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also sections 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Tablet core:

lactose monohydrate
croscarmellose sodium
hydroxypropylcellulose
microcrystalline cellulose
sodium laurilsulfate
magnesium stearate

Film-coat:

lactose monohydrate
hypromellose
triacetin
titanium dioxide (E171)
iron oxide yellow (E172)
talc

7. MANUFACTURER

Eli Lilly Basingstoke UK

8. IMPORTER

Eli Lilly Israel Limited
POB 2160 Herzliya Pitach 46120 Israel

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This leaflet format was set by MoH and its content has been reviewed and approved.