

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg tadalafil.

Excipients: Each coated tablet contains 92 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light orange-yellow and almond shaped tablets, marked "C 2 ½" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

In order for tadalafil 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. CIALIS is available as 2.5, 5, 10, and 20 mg film-coated tablets.

Use in adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.

In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In responder patients to on-demand regimen who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Use in elderly men

Dose adjustments are not required in elderly patients.

Use in men with impaired renal function

Dose 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. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (See sections 4.4 and 5.2).

Use in men with impaired hepatic function

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (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 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (See section 5.2).

Use in men with diabetes

Dose 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

Hypersensitivity to the active substance or to any of the excipients.

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).

Agents for the treatment of erectile dysfunction, including CIALIS, must 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 (< 90/50 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 eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and 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) and as such potentiate the hypotensive effect of nitrates (see section 4.3).

In patients receiving concomitant antihypertensive medicines, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

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.

Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Due to increased tadalafil 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 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 who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

In patients who are taking alpha₁ blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

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 medicines are combined (see section 4.5).

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 rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other substances 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 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 (see section 4.4) 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 (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

In clinical studies, tadalafil (5, 10 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 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-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.

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 (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 medicines, tadalafil 20 mg 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 medicines. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicines.

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.

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg 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 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 medicines.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products 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 (10 mg and 20 mg) 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 (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

CIALIS is not indicated for use by women.

For tadalafil no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. 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 were headache and dyspepsia. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

The table below lists the adverse reactions reported during placebo-controlled clinical trials for registration in patients treated with CIALIS on demand and daily dosing. Adverse reactions are also included that have been reported from postmarketing surveillance in patients taking CIALIS on demand.

Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$) and Not known (events not reported in registration trials cannot be estimated from postmarketing spontaneous reports).

Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1000$)	Not known
<i>System Organ Class: Immune system disorders</i>				
		Hypersensitivity reactions		
<i>System Organ Class: Nervous System disorders</i>				
Headache	Dizziness		Stroke ¹ , Syncope, Transient ischaemic attacks ¹ , Migraine	Seizures, Transient amnesia
<i>System Organ Class: Eye disorders</i>				
		Blurred vision, Sensations described as eye pain, Swelling of eyelids, Conjunctival hyperaemia	Visual field defect	Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion
<i>System Organ Class: Ear and labyrinth disorders</i>				
				Sudden deafness ²
<i>System Organ Class: Cardiac disorders¹</i>				
	Palpitations	Tachycardia	Myocardial infarction	Unstable angina pectoris, Ventricular arrhythmia

<i>System Organ Class: Vascular disorders</i>				
	Flushing	Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), Hypertension		
<i>System Organ Class: Respiratory, thoracic and mediastinal disorders</i>				
	Nasal congestion	Epistaxis		
<i>System Organ Class: Gastrointestinal disorders</i>				
Dyspepsia	Abdominal pain, Gastro-oesophageal reflux			
<i>System Organ Class: Skin and subcutaneous tissue disorders</i>				
		Rash, Urticaria, Hyperhidrosis (sweating)		Stevens-Johnson syndrome, Exfoliative dermatitis
<i>System Organ Class: Musculoskeletal, connective tissue and bone disorders</i>				
	Back pain, Myalgia			
<i>System Organ Class: Reproductive system and breast disorders</i>				
			Prolonged erections	Priapism
<i>System Organ Class: General disorders and administration site conditions</i>				
		Chest pain ¹	Facial oedema	Sudden cardiac death ¹

(1) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (see section 4.4).

(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction, ATC Code: G04BE.

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 on demand. 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.

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 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.

Tadalafil at doses of 2.5, 5, and 10 mg taken once a day has been evaluated in 3 clinical studies involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. Most patients in all three studies were responders to previous on-demand treatment with PDE5 inhibitors. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful attempts were 57 and 67% on CIALIS 5mg, 50% on CIALIS 2.5mg 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 5mg and 2.5mg, respectively, as compared to 28% 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-dose, on demand) of 48% as compared to 17% 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 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 mg-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 pre- 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,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 28 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002
Date of last renewal: 12 November 2007

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg tadalafil.

Excipients: Each coated tablet contains 127 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow and almond shaped tablets, marked "C 5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

In order for tadalafil 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. CIALIS is available as 2.5, 5, 10 and 20 mg film-coated tablets.

Use in adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.

In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In responder patients to on-demand regimen who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Use in elderly men

Dose adjustments are not required in elderly patients.

Use in men with impaired renal function

Dose 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. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (See sections 4.4 and 5.2).

Use in men with impaired hepatic function

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (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 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore, if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (See section 5.2).

Use in men with diabetes

Dose 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

Hypersensitivity to the active substance or to any of the excipients.

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).

Agents for the treatment of erectile dysfunction, including CIALIS, must 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 (< 90/50 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 eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and 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) and as such potentiate the hypotensive effect of nitrates (see section 4.3).

In patients receiving concomitant antihypertensive medicines, tadalafil may induce a blood pressure decrease. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

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.

Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

Due to increased tadalafil 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 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 who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

In patients who are taking alpha₁ blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

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 medicines are combined (see section 4.5).

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 rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other substances 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 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 (see section 4.4) 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 (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

In clinical studies, tadalafil (5, 10 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 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-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.

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 (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 medicines, tadalafil 20 mg 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 medicines. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicines.

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.

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg 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 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 medicines.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products 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 (10 mg and 20 mg) 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 (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

CIALIS is not indicated for use by women.

For tadalafil no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. 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 were headache and dyspepsia. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

The table below lists the adverse reactions reported during placebo-controlled clinical trials for registration in patients treated with CIALIS on demand and daily dosing. Adverse reactions are also included that have been reported from postmarketing surveillance in patients taking CIALIS on demand.

Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$) and

Not known (events not reported in registration trials cannot be estimated postmarketing spontaneous reports)

Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1000$)	Not known
<i>System Organ Class: Immune system disorders</i>				
		Hypersensitivity reactions		
<i>System Organ Class: Nervous System disorders</i>				
Headache	Dizziness		Stroke ¹ , Syncope, Transient ischaemic attacks ¹ , Migraine	Seizures, Transient amnesia
<i>System Organ Class: Eye disorders</i>				
		Blurred vision, Sensations described as eye pain, Swelling of eyelids, Conjunctival hyperaemia	Visual field defect	Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion
<i>System Organ Class: Ear and labyrinth disorders</i>				
				Sudden deafness ²
<i>System Organ Class: Cardiac disorders¹</i>				
	Palpitations	Tachycardia	Myocardial infarction	Unstable angina pectoris, Ventricular arrhythmia

<i>System Organ Class: Vascular disorders</i>				
	Flushing	Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), Hypertension		
<i>System Organ Class: Respiratory, thoracic and mediastinal disorders</i>				
	Nasal congestion	Epistaxis		
<i>System Organ Class: Gastrointestinal disorders</i>				
Dyspepsia	Abdominal pain, Gastro-oesophageal reflux			
<i>System Organ Class: Skin and subcutaneous tissue disorders</i>				
		Rash, Urticaria, Hyperhidrosis (sweating)		Stevens-Johnson syndrome, Exfoliative dermatitis
<i>System Organ Class: Musculoskeletal, connective tissue and bone disorders</i>				
	Back pain, Myalgia			
<i>System Organ Class: Reproductive system and breast disorders</i>				
			Prolonged erections	Priapism
<i>System Organ Class: General disorders and administration site conditions</i>				
		Chest pain ¹	Facial oedema	Sudden cardiac death ¹

(1) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (see section 4.4).

(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction, ATC Code: G04BE.

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 on demand. 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.

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 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.

Tadalafil at doses of 2.5, 5, and 10 mg taken once a day has been evaluated in 3 clinical studies involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. Most patients in all three studies were responders to previous on-demand treatment with PDE5 inhibitors. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful attempts were 57 and 67% on CIALIS 5mg, 50% on CIALIS 2.5mg 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 5mg and 2.5mg, respectively, as compared to 28% 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-dose, on demand) of 48% as compared to 17% 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 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 (5mg -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 pre- 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,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 14 or 28 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.

Grootslag 1-5, NL-3991 RA, Houten

The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/007-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002

Date of last renewal: 12 November 2007

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg tadalafil.

Excipients: Each coated tablet contains 179 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow and almond shaped tablets, marked "C 10" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

In order for tadalafil 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. CIALIS is available as 2.5, 5, 10 and 20 mg film-coated tablets.

Use in adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food.

In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In responder patients to on-demand regimen who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Use in elderly men

Dose adjustments are not required in elderly patients.

Use in men with impaired renal function

Dose 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. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (See sections 4.4 and 5.2)

Use in men with impaired hepatic function

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (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 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (See section 5.2).

Use in men with diabetes

Dose 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

Hypersensitivity to the active substance or to any of the excipients.

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).

Agents for the treatment of erectile dysfunction, including CIALIS, must 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 (< 90/50 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 eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and 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) and as such potentiate the hypotensive effect of nitrates (see section 4.3).

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.

Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is 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 who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

In patients who are taking alpha₁ blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

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 medicines are combined (see section 4.5).

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 rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other substances 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 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 (see section 4.4) 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 (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

In clinical studies, tadalafil (5, 10 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 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 – 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.

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 (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 medicines, tadalafil 20 mg 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 medicines. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicines.

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.

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg 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 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 medicines.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products 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 (10 mg and 20 mg) 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 (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

CIALIS is not indicated for use by women.

For tadalafil no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. 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 were headache and dyspepsia. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

The table below lists the adverse reactions reported during placebo-controlled clinical trials for registration in patients treated with CIALIS on demand and daily dosing. Adverse reactions are also included that have been reported from postmarketing surveillance in patients taking CIALIS on demand.

Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$) and Not known (events not reported in registration trials cannot be estimated from postmarketing spontaneous reports)

Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1000$)	Not known
<i>System Organ Class: Immune system disorders</i>				
		Hypersensitivity reactions		
<i>System Organ Class: Nervous System disorders</i>				
Headache	Dizziness		Stroke ¹ , Syncope, Transient ischaemic attacks ¹ , Migraine	Seizures, Transient amnesia
<i>System Organ Class: Eye disorders</i>				
		Blurred vision, Sensations described as eye pain, Swelling of eyelids, Conjunctival hyperaemia	Visual field defect	Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion
<i>System Organ Class: Ear and labyrinth disorders</i>				
				Sudden deafness ²
<i>System Organ Class: Cardiac disorders¹</i>				
	Palpitations	Tachycardia	Myocardial infarction	Unstable angina pectoris, Ventricular arrhythmia

<i>System Organ Class: Vascular disorders</i>				
	Flushing	Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), Hypertension		
<i>System Organ Class: Respiratory, thoracic and mediastinal disorders</i>				
	Nasal congestion	Epistaxis		
<i>System Organ Class: Gastrointestinal disorders</i>				
Dyspepsia	Abdominal pain, Gastro-oesophageal reflux			
<i>System Organ Class: Skin and subcutaneous tissue disorders</i>				
		Rash, Urticaria, Hyperhydrosis (sweating)		Stevens-Johnson syndrome, Exfoliative dermatitis
<i>System Organ Class: Musculoskeletal, connective tissue and bone disorders</i>				
	Back pain, Myalgia			
<i>System Organ Class: Reproductive system and breast disorders</i>				
			Prolonged erections	Priapism
<i>System Organ Class: General disorders and administration site conditions</i>				
		Chest pain ¹	Facial oedema	Sudden cardiac death ¹

(1) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (See section 4.4).

(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction, ATC Code G04BE.

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. 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.

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 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.

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 21-86 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-dose, on demand) of 48% as compared to 17% 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 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 (5mg - 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). If CIALIS is 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 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 1000 mg/kg/day tadalafil. In a rat pre- 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,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 4 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.

Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002

Date of last renewal: 12 November 2007

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg tadalafil.

Excipients: Each coated tablet contains 245 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow and almond shaped tablets, marked "C 20" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

In order for tadalafil 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. CIALIS is available as 2.5, 5, 10 and 20 mg film-coated tablets.

Use in adult men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried.

It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In responder patients to on-demand regimen who anticipate a frequent use of CIALIS (i.e., at least twice weekly) a once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician's judgement.

In these patients the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Use in elderly men

Dose adjustments are not required in elderly patients.

Use in men with impaired renal function

Dose 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. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment. (See sections 4.4 and 5.2)

Use in men with impaired hepatic function

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (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 10 mg of tadalafil to patients with hepatic impairment. Once-a-day dosing has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (See section 5.2).

Use in men with diabetes

Dose 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

Hypersensitivity to the active substance or to any of the excipients.

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).

Agents for the treatment of erectile dysfunction, including CIALIS, must 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 (< 90/50 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 eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and 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) and as such potentiate the hypotensive effect of nitrates (see section 4.3).

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.

Visual defects and cases of NAION have been reported in connection with the intake of CIALIS and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking CIALIS and consult a physician immediately (see section 4.3).

There is limited clinical data on the safety of single-dose administration of CIALIS in patients with severe hepatic insufficiency (Child-Pugh Class C). If CIALIS is 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 who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

In patients who are taking alpha₁ blockers concomitant administration of CIALIS may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

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 medicines are combined (see section 4.5).

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 rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other substances 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 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 (see section 4.4). 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 (10 mg). This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4 such as phenobarbital, phenytoin and carbamazepine, may also decrease plasma concentrations of tadalafil.

Effects of tadalafil on other medicinal products

In clinical studies, tadalafil (5, 10 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 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 – 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.

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 (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 medicines, tadalafil 20 mg 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 medicines. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicines.

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.

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with tadalafil (10 mg 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 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 medicines.

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of medicinal products 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 (10 mg and 20 mg) 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 (10 mg and 20 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

CIALIS is not indicated for use by women.

For tadalafil no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. 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. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

The table below lists the adverse reactions reported during placebo-controlled clinical trials for registration in patients treated with CIALIS on demand and daily dosing. Adverse reactions are also included that have been reported from postmarketing surveillance in patients taking CIALIS on demand.

Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1000$), Very Rare ($< 1/10,000$) and Not known (events not reported in registration trials cannot be estimated from postmarketing spontaneous reports)

Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1000$)	Not known
<i>System Organ Class: Immune system disorders</i>				
		Hypersensitivity reactions		
<i>System Organ Class: Nervous System disorders</i>				
Headache	Dizziness		Stroke ¹ , Syncope, Transient ischaemic attacks ¹ , Migraine	Seizures, Transient amnesia
<i>System Organ Class: Eye disorders</i>				
		Blurred vision, Sensations described as eye pain, Swelling of eyelids, Conjunctival hyperaemia	Visual field defect	Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion
<i>System Organ Class: Ear and labyrinth disorders</i>				
				Sudden deafness ²
<i>System Organ Class: Cardiac disorders¹</i>				
	Palpitations	Tachycardia	Myocardial infarction	Unstable angina pectoris, Ventricular arrhythmia

<i>System Organ Class: Vascular disorders</i>				
	Flushing	Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), Hypertension		
<i>System Organ Class: Respiratory, thoracic and mediastinal disorders</i>				
	Nasal congestion	Epistaxis		
<i>System Organ Class: Gastrointestinal disorders</i>				
Dyspepsia	Abdominal pain, Gastro-oesophageal reflux			
<i>System Organ Class: Skin and subcutaneous tissue disorders</i>				
		Rash, Urticaria, Hyperhydrosis (sweating)		Stevens-Johnson syndrome, Exfoliative dermatitis
<i>System Organ Class: Musculoskeletal, connective tissue and bone disorders</i>				
	Back pain, Myalgia			
<i>System Organ Class: Reproductive system and breast disorders</i>				
			Prolonged erections	Priapism
<i>System Organ Class: General disorders and administration site conditions</i>				
		Chest pain ¹	Facial oedema	Sudden cardiac death ¹

(1) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors (See section 4.4).

(2) Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil.

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction, ATC Code G04BE.

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. 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.

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 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.

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 21-86 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-dose, on demand) of 48% as compared to 17% 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 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 (5-20 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). If CIALIS is 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 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 1000 mg/kg/day tadalafil. In a rat pre- 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,
hydroxypropylcellulose,
microcrystalline cellulose,
sodium laurilsulfate,
magnesium stearate.

Film-coat:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminium/PVC/PE/PCTFE blisters in cartons of 2, 4, 8 and 12 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.

Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/002-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2002

Date of last renewal: 12 November 2007

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription

• CONDITIONS OR RESTRICTIONS WITH REGARDS TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The Marketing Authorisation Holder must ensure that the system of pharmacovigilance, as described in version 1 presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market

Risk Management Plan

The Marketing Authorisation Holder commits to performing the studies additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 of the Risk Management Plan (RPM) presented in Module 1.8.2. of the Marketing Authorisation and subsequent updates of the RPM agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimization activities.
- within 60 days of an important (pharmacovigilance or risk minimization) milestone being reached.
- at the request of the EMEA.

PSUR

The Marketing Authorisation Holder will continue to submit yearly PSURs unless otherwise specified by the CHMP.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 2.5 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg tadalafil

3. LIST OF EXCIPIENTS

lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral once-a-day use. Read the package leaflet before use.

How to take CIALIS Once-A-Day

1. Start with the pill from the blister pack that corresponds with the day you start taking CIALIS.
2. Take CIALIS with water every day at approximately the same time, either with or without food.
3. When taken once a day CIALIS allows you to obtain an erection, when sexually stimulated, at any time point during the 24 hours of the day. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

- Always take CIALIS exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
- Drinking alcohol may affect your ability to get an erection so avoid excessive drinking with CIALIS.
- You should NOT take CIALIS more than once a day. If you take more than you should, tell your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/006

13. BATCH NUMBER

Lot.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cialis 2.5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 5 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg tadalafil

3. LIST OF EXCIPIENTS

lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral once-a-day use. Read the package leaflet before use.

How to take CIALIS Once-A-Day

1. Start with the pill from the blister pack that corresponds with the day you start taking CIALIS.
2. Take CIALIS with water every day at approximately the same time, either with or without food.
3. When taken once a day CIALIS allows you to obtain an erection, when sexually stimulated, at any time point during the 24 hours of the day. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

- Always take CIALIS exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
- Drinking alcohol may affect your ability to get an erection so avoid excessive drinking with CIALIS.
- You should NOT take CIALIS more than once a day. If you take more than you should, tell your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP. {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/007-008

13. BATCH NUMBER

Lot.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cialis 5 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 10 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg tadalafil

3. LIST OF EXCIPIENTS

lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/001

13. BATCH NUMBER

Lot.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cialis 10 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 20 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg tadalafil

3. LIST OF EXCIPIENTS

lactose monohydrate

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Grootslag 1-5, NL-3991 RA, Houten
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/237/002-005

13. BATCH NUMBER

Lot.

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cialis 20 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 2.5 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot.

5. OTHER

MON, TUE, WED, THU, FRI, SAT, SUN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTERS**

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 5 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot.

5. OTHER

MON, TUE, WED, THU, FRI, SAT, SUN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 10 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot.

5. OTHER

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTER**

1. NAME OF THE MEDICINAL PRODUCT

CIALIS 20 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot.

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

CIALIS 2.5 mg film-coated tablets tadalafil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What CIALIS is and what it is used for
2. Before you take CIALIS
3. How to take CIALIS
4. Possible side effects
5. How to store CIALIS
6. Further information

1. WHAT CIALIS IS AND WHAT IT IS USED FOR

CIALIS is a treatment for men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

CIALIS belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation CIALIS works by helping the blood vessels in your penis to relax, allowing the flow of blood into your penis. The result of this is improved erectile function. CIALIS will not help you if you do not have erectile dysfunction.

It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

2. BEFORE YOU TAKE CIALIS

Do not take CIALIS

- if you are allergic (hypersensitive) to tadalafil or any of the other ingredients of CIALIS.
- if you are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite. This is a group of medicines (“nitrates”) used in the treatment of angina pectoris (“chest pain”). CIALIS has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have serious heart disease or have had a recent heart attack.
- if you have had a recent stroke.
- if you have low blood pressure or uncontrolled high blood pressure.

- if you have ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition sometimes described as “stroke of the eye”.

Take special care with CIALIS

Be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on your heart. If you have a heart problem you should tell your doctor.

The following are reasons why CIALIS may also not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You have sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells) or any deformation of your penis.
- You have a serious liver problem.
- You have a severe kidney problem.

It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

If you experience sudden decrease or loss of vision, stop taking CIALIS and contact your doctor immediately.

CIALIS is not intended for use by women or by adolescents under the age of 18.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, because they might interact.

This is particularly important if you are treated with nitrates as you should not take CIALIS if you are taking these medicines.

A type of medicine called an alpha blocker is sometimes used to treat high blood pressure and enlarged prostate. Tell your doctor if you are being treated for either of these conditions or if you take other medicines to treat high blood pressure.

If you are taking medicines that can inhibit an enzyme called CYP3A4 (for example ketoconazole or protease inhibitors for treatment of HIV) the frequency of side effects might increase.

Do not take CIALIS with other medicines if your doctor tells you that you may not.

You should not use CIALIS together with any other treatments for erectile dysfunction.

Taking CIALIS with food and drink

You may take CIALIS with or without food.

Information on the effect of alcohol is in section 3.

Driving and using machines

Some men taking CIALIS in clinical studies have reported dizziness. Check carefully how you react to the medicines before driving or using any machinery.

Important information about some of the ingredients of CIALIS:

CIALIS contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CIALIS

Always take CIALIS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Once a day dosing of CIALIS may be useful to men who anticipate having sexual activity two or more times per week. The recommended dose is one 5 mg tablet taken once a day at approximately the same time of the day. Your doctor may adjust the dose to 2.5 mg based on your response to CIALIS. CIALIS tablets are for oral use. Swallow the tablet whole with some water. You may take CIALIS with or without food.

When taken once a day CIALIS allows you to obtain an erection, when sexually stimulated, at any time point during the 24 hours of the day. It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

Drinking alcohol may affect your ability to get an erection. Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take CIALIS, avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up.

You should NOT take CIALIS more than once a day.

If you take more CIALIS than you should

Tell your doctor.

If you forget to take CIALIS

Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CIALIS can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

In this leaflet, when a side effect is described as “very common” this means that it has been reported in at least 1 in 10 patients taking the medicine. When a side effect is described as “common” this means that it has been reported in more than 1 in every 100 patients but less than 1 in every 10 patients. When a side effect is described as “uncommon”, this means it has been reported in more than 1 in every 1,000 patients, but less than 1 in every 100 patients. When a side effect is described as “rare”, this means it has been reported in more than 1 in every 10,000 patients, but less than 1 in every 1,000 patients.

Very commonly reported side effects in patients taking CIALIS were headache and indigestion.

Commonly reported side effects in patients taking CIALIS include back pain, muscle aches, facial flushing, nasal congestion, dizziness, pounding heartbeat sensation, abdominal pain and reflux.

Uncommon side effects are allergic reactions including rashes and hives, blurred vision, swelling of the eyelids, eye pain, red eyes, increased sweating, nose bleeds, a fast heart rate, high blood pressure, low blood pressure and chest pain. In case of chest pain occurring during or after sexual activity you should NOT use nitrates but you should seek immediate medical assistance.

Rare side effects in patients taking CIALIS include fainting, migraine and swelling of the face.

In rare instances it is possible that a prolonged and possibly painful erection may occur after taking CIALIS. If you have such an erection, which lasts continuously for more than 4 hours, you should contact a doctor immediately.

Heart attack and stroke have also been reported rarely in men taking CIALIS. Most, but not all of these men had known heart problems before taking this medicine. It is not possible to determine whether these events were directly related to CIALIS.

Partial, sudden, temporary, or permanent decrease or loss of vision in one or both eyes has been rarely reported.

Some additional side effects have been reported in men taking CIALIS that were not seen in clinical trials and their incidence is unknown. These include seizures and passing memory loss, some disorders affecting blood flow to the eyes, irregular heartbeats and angina, serious skin rashes and sudden cardiac death. Sudden decrease or loss of hearing has been reported.

Effects were seen in one animal species that might indicate impairment of fertility. Subsequent studies in man suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CIALIS

Keep out of the reach and sight of children.

Do not use CIALIS after the expiry date stated on the carton and blister.

Store in the original package in order to protect from moisture. Do not store above 30°C

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CIALIS contains

The active substance is tadalafil. Each tablet contains 2.5 mg of tadalafil.

The other ingredients are:

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), iron oxide red (E172) talc.

What CIALIS looks like and contents of the pack

CIALIS 2.5 mg strength comes as orange-yellow film-coated tablets. They are in the shape of almonds and have "C 2 ½" marked on one side.

CIALIS 2.5 mg is available in blister packs containing 28 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands

Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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United Kingdom

Eli Lilly and Company Limited
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Lietuva

Eli Lilly Holdings Limited atstovybė
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This leaflet was last approved in {date}

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

CIALIS 5 mg film-coated tablets tadalafil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What CIALIS is and what it is used for
2. Before you take CIALIS
3. How to take CIALIS
4. Possible side effects
5. How to store CIALIS
6. Further information

1. WHAT CIALIS IS AND WHAT IT IS USED FOR

CIALIS is a treatment for men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

CIALIS belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation CIALIS works by helping the blood vessels in your penis to relax, allowing the flow of blood into your penis. The result of this is improved erectile function. CIALIS will not help you if you do not have erectile dysfunction.

It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

2. BEFORE YOU TAKE CIALIS

Do not take CIALIS

- if you are allergic (hypersensitive) to tadalafil or any of the other ingredients of CIALIS.
- if you are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite. This is a group of medicines (“nitrates”) used in the treatment of angina pectoris (“chest pain”). CIALIS has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have serious heart disease or have had a recent heart attack.
- if you have had a recent stroke.
- if you have low blood pressure or uncontrolled high blood pressure.

- if you have ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition sometimes described as “stroke of the eye”.

Take special care with CIALIS

Be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on your heart. If you have a heart problem you should tell your doctor.

The following are reasons why CIALIS may also not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You have sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells) or any deformation of your penis.
- You have a serious liver problem.
- You have a severe kidney problem.

It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy

If you experience sudden decrease or loss of vision, stop taking CIALIS and contact your doctor immediately.

CIALIS is not intended for use by women or by adolescents under the age of 18.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, because they might interact.

This is particularly important if you are treated with nitrates as you should not take CIALIS if you are taking these medicines.

A type of medicine called an alpha blocker is sometimes used to treat high blood pressure and enlarged prostate. Tell your doctor if you are being treated for either of these conditions or if you take other medicines to treat high blood pressure.

If you are taking medicines that can inhibit an enzyme called CYP3A4 (for example ketoconazole or protease inhibitors for treatment of HIV) the frequency of side effects might increase.

Do not take CIALIS with other medicines if your doctor tells you that you may not.

You should not use CIALIS together with any other treatments for erectile dysfunction.

Taking CIALIS with food and drink

You may take CIALIS with or without food.

Information on the effect of alcohol is in section 3.

Driving and using machines

Some men taking CIALIS in clinical studies have reported dizziness. Check carefully how you react to the medicines before driving or using any machinery.

Important information about some of the ingredients of CIALIS:

CIALIS contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CIALIS

Always take CIALIS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Once a day dosing of CIALIS may be useful to men who anticipate having sexual activity two or more times per week. The recommended dose is one 5 mg tablet taken once a day at approximately the same time of the day. Your doctor may adjust the dose to 2.5 mg based on your response to CIALIS. CIALIS tablets are for oral use. Swallow the tablet whole with some water. You may take CIALIS with or without food.

When taken once a day CIALIS allows you to obtain an erection, when sexually stimulated, at any time point during the 24 hours of the day. It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

Drinking alcohol may affect your ability to get an erection. Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take CIALIS, avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up.

You should NOT take CIALIS more than once a day.

If you take more CIALIS than you should

Tell your doctor.

If you forget to take CIALIS

Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CIALIS can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

In this leaflet, when a side effect is described as “very common” this means that it has been reported in at least 1 in 10 patients taking the medicine. When a side effect is described as “common” this means that it has been reported in more than 1 in every 100 patients but less than 1 in every 10 patients. When a side effect is described as “uncommon”, this means it has been reported in more than 1 in every 1,000 patients, but less than 1 in every 100 patients. When a side effect is described as “rare”, this means it has been reported in more than 1 in every 10,000 patients, but less than 1 in every 1,000 patients.

Very commonly reported side effects in patients taking CIALIS were headache and indigestion.

Commonly reported side effects in patients taking CIALIS include back pain, muscle aches, facial flushing, nasal congestion, dizziness, pounding heartbeat sensation, abdominal pain and reflux.

Uncommon side effects are allergic reactions including rashes and hives, blurred vision, swelling of the eyelids, eye pain, red eyes, increased sweating, nose bleeds, a fast heart rate, high blood pressure, low blood pressure and chest pain. In case of chest pain occurring during or after sexual activity you should NOT use nitrates but you should seek immediate medical assistance.

Rare side effects in patients taking CIALIS include fainting, migraine and swelling of the face.

In rare instances it is possible that a prolonged and possibly painful erection may occur after taking CIALIS. If you have such an erection, which lasts continuously for more than 4 hours, you should contact a doctor immediately.

Heart attack and stroke have also been reported rarely in men taking CIALIS. Most, but not all of these men had known heart problems before taking this medicine. It is not possible to determine whether these events were directly related to CIALIS.

Partial, sudden, temporary, or permanent decrease or loss of vision in one or both eyes has been rarely reported.

Some additional side effects have been reported in men taking CIALIS that were not seen in clinical trials and their incidence is unknown. These include seizures and passing memory loss, some disorders affecting blood flow to the eyes, irregular heartbeats and angina, serious skin rashes and sudden cardiac death. Sudden decrease or loss of hearing has been reported.

Effects were seen in one animal species that might indicate impairment of fertility. Subsequent studies in man suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CIALIS

Keep out of the reach and sight of children.

Do not use CIALIS after the expiry date stated on the carton and blister.

Store in the original package in order to protect from moisture. Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CIALIS contains

The active substance is tadalafil. Each tablet contains 5 mg of tadalafil.

The other ingredients are:

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.

What CIALIS looks like and contents of the pack

CIALIS 5 mg strength comes as light yellow film-coated tablets. They are in the shape of almonds and have "C 5" marked on one side.

CIALIS 5 mg is available in blister packs containing 14 or 28 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands

Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {date}

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>

PACKAGE LEAFLET: INFORMATION FOR THE USER

CIALIS 10 mg film-coated tablets tadalafil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What CIALIS is and what it is used for
2. Before you take CIALIS
3. How to take CIALIS
4. Possible side effects
5. How to store CIALIS
6. Further information

1. WHAT CIALIS IS AND WHAT IT IS USED FOR

CIALIS is a treatment for men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

CIALIS belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation CIALIS works by helping the blood vessels in your penis to relax, allowing the flow of blood into your penis. The result of this is improved erectile function. CIALIS will not help you if you do not have erectile dysfunction.

It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

2. BEFORE YOU TAKE CIALIS

Do not take CIALIS

- if you are allergic (hypersensitive) to tadalafil or any of the other ingredients of CIALIS.
- if you are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite. This is a group of medicines (“nitrates”) used in the treatment of angina pectoris (“chest pain”). CIALIS has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have serious heart disease or have had a recent heart attack.
- if you have had a recent stroke
- if you have low blood pressure or uncontrolled high blood pressure.
- if you have ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition sometimes described as “stroke of the eye”.

Take special care with CIALIS

Be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on your heart. If you have a heart problem you should tell your doctor.

The following are reasons why CIALIS may also not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You have sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells) or any deformation of your penis.
- You have a serious liver problem.
- You have a severe kidney problem.

It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

If you experience sudden decrease or loss of vision, stop taking CIALIS and contact your doctor immediately.

CIALIS is not intended for use by women or by adolescents under the age of 18.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicine, including medicines obtained without prescription, because they might interact.

This is particularly important if you are treated with nitrates as you should not take CIALIS if you are taking these medicines.

A type of medicine called an alpha blocker is sometimes used to treat high blood pressure and enlarged prostate. Tell your doctor if you are being treated for either of these conditions or if you take other medicines to treat high blood pressure.

If you are taking medicines that can inhibit an enzyme called CYP3A4 (for example ketoconazole or protease inhibitors for treatment of HIV) the frequency of side effects might increase.

Do not take CIALIS with other medicines if your doctor tells you that you may not.

You should not use CIALIS together with any other treatments for erectile dysfunction.

Taking CIALIS with food and drink

You may take CIALIS with or without food.

Information on the effect of alcohol is in section 3.

Driving and using machines

Some men taking CIALIS in clinical studies have reported dizziness. Check carefully how you react to the medicines before driving or using any machinery.

Important information about some of the ingredients of CIALIS:

CIALIS contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CIALIS

Always take CIALIS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended starting dose is one 10 mg tablet before sexual activity. If the effect of this dose is too weak your doctor may increase the dose to 20 mg. CIALIS tablets are for oral use. Swallow the tablet whole with some water. You may take CIALIS with or without food.

You may take a CIALIS tablet at least 30 minutes before sexual activity. CIALIS may still be effective up to 36 hours after taking the tablet. It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

Drinking alcohol may affect your ability to get an erection. Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take CIALIS, avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up.

You should NOT take CIALIS more than once a day. CIALIS 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not recommended for continuous daily use.

If you take more CIALIS than you should

Tell your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CIALIS can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

In this leaflet, when a side effect is described as “very common” this means that it has been reported in at least 1 in 10 patients taking the medicine. When a side effect is described as “common” this means that it has been reported in more than 1 in every 100 patients but less than 1 in every 10 patients. When a side effect is described as “uncommon”, this means it has been reported in more than 1 in every 1,000 patients, but less than 1 in every 100 patients. When a side effect is described as “rare”, this means it has been reported in more than 1 in every 10,000 patients, but less than 1 in every 1,000 patients.

Very commonly reported side effect in patients taking CIALIS were headache and indigestion.

Commonly reported side effects in patients taking CIALIS include back pain, muscle aches, facial flushing, nasal congestion, dizziness, pounding heartbeat sensation, abdominal pain and reflux.

Uncommon side effects are allergic reactions including rashes and hives, blurred vision, swelling of the eyelids, eye pain, red eyes, increased sweating, nose bleeds, a fast heart rate, high blood pressure, low blood pressure and chest pain. In case of chest pain occurring during or after sexual activity you should NOT use nitrates but you should seek immediate medical assistance.

Rare side effects in patients taking CIALIS include fainting, migraine and swelling of the face.

In rare instances it is possible that a prolonged and possibly painful erection may occur after taking CIALIS. If you have such an erection, which lasts continuously for more than 4 hours, you should contact a doctor immediately.

Heart attack and stroke have also been reported rarely in men taking CIALIS. Most, but not all of these men had known heart problems before taking this medicine. It is not possible to determine whether these events were directly related to CIALIS.

Partial, sudden, temporary, or permanent decrease or loss of vision in one or both eyes has been rarely reported.

Some additional side effects have been reported in men taking CIALIS that were not seen in clinical trials and their incidence is unknown. These include seizures and passing memory loss, some disorders affecting blood flow to the eyes, irregular heartbeats and angina, serious skin rashes and sudden cardiac death. Sudden decrease or loss of hearing has been reported.

Effects were seen in one animal species that might indicate impairment of fertility. Subsequent studies in man suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CIALIS

Keep out of the reach and sight of children.

Do not use CIALIS after the expiry date stated on the carton and blister.

Store in the original package in order to protect from moisture. Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CIALIS contains

The active substance is tadalafil. Each tablet contains 10 mg of tadalafil.

The other ingredients are:

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.

What CIALIS looks like and contents of the pack

CIALIS 10 mg comes as light yellow film-coated tablets. They are in the shape of almonds and have "C 10" marked on one side.

Cialis 10 mg is available in blister packs containing 4 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA, Houten, The Netherlands

Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {date}

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>

PACKAGE LEAFLET : INFORMATION FOR THE USER

CIALIS 20 mg film-coated tablets tadalafil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What CIALIS is and what it is used for
2. Before you take CIALIS
3. How to take CIALIS
4. Possible side effects
5. How to store CIALIS
6. Further information

1. WHAT CIALIS IS AND WHAT IT IS USED FOR

CIALIS is a treatment for men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

CIALIS belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation CIALIS works by helping the blood vessels in your penis to relax, allowing the flow of blood into your penis. The result of this is improved erectile function. CIALIS will not help you if you do not have erectile dysfunction.

It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

2. BEFORE YOU TAKE CIALIS

Do not take CIALIS

- if you are allergic (hypersensitive) to tadalafil or any of the other ingredients of CIALIS.
- if you are taking any form of organic nitrate or nitric oxide donors such as amyl nitrite. This is a group of medicines (“nitrates”) used in the treatment of angina pectoris (“chest pain”). CIALIS has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- if you have serious heart disease or have had a recent heart attack.
- if you have had a recent stroke.
- if you have low blood pressure or uncontrolled high blood pressure.
- if you have ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.

Take special care with CIALIS

Be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on your heart. If you have a heart problem you should tell your doctor.

The following are reasons why CIALIS may also not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You have sickle cell anaemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), leukaemia (cancer of the blood cells) or any deformation of your penis.
- You have a serious liver problem.
- You have a severe kidney problem

It is not known if CIALIS is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

If you experience sudden decrease or loss of vision, stop taking CIALIS and contact your doctor immediately.

CIALIS is not intended for use by women or by adolescents under the age of 18.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without prescription, because they might interact.

This is particularly important if you are treated with nitrates as you should not take CIALIS if you are taking these medicines.

A type of medicine called an alpha blocker is sometimes used to treat high blood pressure and enlarged prostate. Tell your doctor if you are being treated for either of these conditions or if you take other medicines to treat high blood pressure.

If you are taking medicines that can inhibit an enzyme called CYP3A4 (for example ketoconazole or protease inhibitors for treatment of HIV) the frequency of side effects might increase.

Do not take CIALIS with other medicines if your doctor tells you that you may not.

You should not use CIALIS together with any other treatments for erectile dysfunction.

Taking CIALIS with food and drink

You may take CIALIS with or without food.

Information on the effect of alcohol is in section 3.

Driving and using machines

Some men taking CIALIS in clinical studies have reported dizziness. Check carefully how you react to the medicines before driving or using any machinery.

Important information about some of the ingredients of CIALIS:

CIALIS contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CIALIS

Always take CIALIS exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended starting dose is one 10 mg tablet before sexual activity. If the effect of this dose is too weak your doctor may increase the dose to 20 mg. CIALIS tablets are for oral use. Swallow the tablet whole with some water. You may take CIALIS with or without food.

You may take a CIALIS tablet at least 30 minutes before sexual activity. CIALIS may still be effective up to 36 hours after taking the tablet. It is important to note that CIALIS does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking a medicine for erectile dysfunction.

Drinking alcohol may affect your ability to get an erection. Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take CIALIS, avoid excessive drinking (blood alcohol level of 0.08% or greater), since this may increase the risk of dizziness when standing up.

You should NOT take CIALIS more than once a day. CIALIS 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not recommended for continuous daily use.

If you take more CIALIS than you should

Tell your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, CIALIS can cause side effects, although not everybody gets them. These effects are normally mild to moderate in nature.

In this leaflet, when a side effect is described as “very common” this means that it has been reported in at least 1 in 10 patients taking the medicine. When a side effect is described as “common” this means that it has been reported in more than 1 in every 100 patients but less than 1 in every 10 patients. When a side effect is described as “uncommon”, this means it has been reported in more than 1 in every 1,000 patients, but less than 1 in every 100 patients. When a side effect is described as “rare”, this means it has been reported in more than 1 in every 10,000 patients, but less than 1 in every 1,000 patients.

Very commonly reported side effect in patients taking CIALIS were headache and indigestion.

Commonly reported side effects in patients taking CIALIS include back pain, muscle aches, facial flushing, nasal congestion, dizziness, pounding heartbeat sensation, abdominal pain and reflux.

Uncommon side effects are allergic reactions including rashes and hives, blurred vision, swelling of the eyelids, eye pain, red eyes, increased sweating, nose bleeds, a fast heart rate, high blood pressure, low blood pressure and chest pain. In case of chest pain occurring during or after sexual activity you should NOT use nitrates but you should seek immediate medical assistance.

Rare side effects in patients taking CIALIS include fainting, migraine and swelling of the face.

In rare instances it is possible that a prolonged and possibly painful erection may occur after taking CIALIS. If you have such an erection, which lasts continuously for more than 4 hours, you should contact a doctor immediately.

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Effects were seen in one animal species that might indicate impairment of fertility. Subsequent studies in man suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CIALIS

Keep out of the reach and sight of children.

Do not use CIALIS after the expiry date stated on the carton and blister.

Store in the original package in order to protect from moisture. Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CIALIS contains

The active substance is tadalafil. Each tablet contains 20 mg of tadalafil.

The other ingredients are:

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.

What CIALIS looks like and contents of the pack

CIALIS 20 mg comes as yellow film-coated tablets. They are in the shape of almonds and have "C 20" marked on one side.

CIALIS 20 mg is available in blister packs containing 2, 4, 8 or 12 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer: Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

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