ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg tadalafil.

Excipient with known effect

Each coated tablet contains 87 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light orange-yellow and almond shaped tablets of 8.58 mm by 5.23 mm, marked "C 2 ½" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

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

Tadalafil Lilly is not indicated for use by women.

4.2 Posology and method of administration

Posology

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 patients who anticipate a frequent use of Tadalafil Lilly (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil Lilly 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.

Special populations

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
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).

Men with hepatic impairment
The recommended dose of Tadalafil Lilly is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil Lilly 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 sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

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

Method of administration

Oral use.

Tadalafil Lilly is available as 2.5, 5, 10, and 20 mg film-coated tablets.

The tablets should be swallowed whole with water, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Tadalafil Lilly, 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.

Tadalafil Lilly is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous Phosphodiesterase-5 (PDE5) inhibitor exposure (see section 4.4).

The co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with Tadalafil Lilly

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 potentiates the hypotensive effect of nitrates (see section 4.3).

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 Tadalafil Lilly is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular

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 Tadalafil Lilly, to sexual activity, or to a combination of these or other factors.

In patients receiving concomitant antihypertensive medicinal products, 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.

In patients who are taking alpha$_1$ blockers, concomitant administration of Tadalafil Lilly may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of Tadalafil Lilly and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking Tadalafil Lilly and consult a physician immediately (see section 4.3).

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history)

patients should be advised to stop taking tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of Tadalafil Lilly is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of Tadalafil Lilly in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If Tadalafil Lilly is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis

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.

Tadalafil Lilly, 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).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing Tadalafil Lilly to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

Tadalafil Lilly and other treatments for erectile dysfunction

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

Lactose

Tadalafil Lilly contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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

Cytochrome P450 inhibitors
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 adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of medicinal product interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
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

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical trial 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 Tadalafil Lilly (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 Tadalafil Lilly before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).

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

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose

blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat
Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
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 maximise 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).

Cytochrome P450 metabolised medicinal products
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.

CYP2C9 substrates (e.g. R-warfarin)
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.

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

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

Tadalafil Lilly is not indicated for use by women.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tadalafil Lilly during pregnancy.

Breast-feeding

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

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking Tadalafil Lilly for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadalafil Lilly. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadalafil Lilly once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 8 022 patients on Tadalafil Lilly and

4 422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

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

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity reactions	Angioedema[2]	
Nervous system disorders		Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia	
Eye disorders			Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]	Central serous chorioretinopathy
Ear and labyrinth disorders			Tinnitus	Sudden hearing loss	
Cardiac disorders[1]			Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]	
Vascular disorders		Flushing	Hypotension[3], Hypertension		
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea, Epistaxis		

Gastrointestinal disorders		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux		
Skin and subcutaneous tissue disorders			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)	
Musculoskeletal, connective tissue and bone disorders		Back pain, Myalgia, Pain in extremity			
Renal and urinary disorders			Haematuria		
Reproductive system and breast disorders			Prolonged erections	Priapism, Penile haemorrhage, Haematospermia	
General disorders and administration site conditions			Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1, 2]	

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Three clinical studies were conducted in 1 054 patients in an at-home setting to define the period of responsiveness to Tadalafil Lilly 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 Tadalafil Lilly 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 was initially 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. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67 % on Tadalafil Lilly 5 mg, 50 % on Tadalafil Lilly 2.5 mg as compared to 31 and 37 % with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46 % on Tadalafil Lilly 5 mg and 2.5 mg, respectively, as compared to 28 % with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naïve to PDE5 inhibitors were randomised to Tadalafil Lilly 5 mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68 % for Tadalafil Lilly patients compared to 52 % for patients on 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.

Paediatric population

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

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 Tadalafil Lilly 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 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of Tadalafil Lilly 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 Tadalafil Lilly 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 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance 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 blisters in cartons of 28 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017
Date of latest renewal: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg tadalafil.

Excipient with known effect

Each coated tablet contains 121 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light yellow and almond shaped tablets of 9.59 mm by 5.85 mm, marked "C 5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

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

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult males.

Tadalafil Lilly is not indicated for use by women.

4.2 Posology and method of administration

Posology

Erectile dysfunction 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 patients who anticipate a frequent use of Tadalafil Lilly (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil Lilly 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.

Benign prostatic hyperplasia in adult men
The recommended dose is 5 mg, taken at approximately the same time every day with or without food. For adult men being treated for both benign prostatic hyperplasia and erectile dysfunction the recommended dose is also 5 mg taken at approximately the same time every day. Patients who are unable to tolerate tadalafil 5 mg for the treatment of benign prostatic hyperplasia should consider an alternative therapy as the efficacy of tadalafil 2.5 mg for the treatment of benign prostatic hyperplasia has not been demonstrated.

Special populations

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
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 for on-demand treatment.

Once-a-day dosing of 2.5 or 5 mg tadalafil both for the treatment of erectile dysfunction or benign prostatic hyperplasia is not recommended in patients with severe renal impairment (see sections 4. 4 and 5.2).

Men with hepatic impairment
For the treatment of erectile dysfunction using on-demand Tadalafil Lilly the recommended dose of Tadalafil Lilly is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil Lilly 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 of Tadalafil Lilly both for the treatment of erectile dysfunction and benign prostatic hyperplasia 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 sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

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

Method of administration

Oral use.

Tadalafil Lilly is available as 2.5, 5, 10, and 20 mg film-coated tablets.

The tablets should be swallowed whole with water, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Tadalafil Lilly, 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.

Tadalafil Lilly is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous Phosphodiesterase-5 (PDE5) inhibitor exposure (see section 4.4).

The co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with Tadalafil Lilly

A medical history and physical examination should be undertaken to diagnose erectile dysfunction or benign prostatic hyperplasia 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 potentiates the hypotensive effect of nitrates (see section 4.3).

Prior to initiating treatment with tadalafil for benign prostatic hyperplasia patients should be examined to rule out the presence of carcinoma of the prostate and carefully assessed for cardiovascular conditions (see section 4.3).

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 Tadalafil Lilly is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular

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 Tadalafil Lilly, to sexual activity, or to a combination of these or other factors.

In patients receiving concomitant antihypertensive medicinal products, 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.

In patients who are taking alpha$_1$ blockers, concomitant administration of Tadalafil Lilly may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of Tadalafil Lilly and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking Tadalafil Lilly and consult a physician immediately (see section 4.3).

Decreased or sudden hearing loss

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

Renal and hepatic impairment

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of Tadalafil Lilly is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of Tadalafil Lilly in patients with severe hepatic insufficiency (Child-Pugh Class C). Once-a-day administration either for the treatment of erectile dysfunction or benign prostatic hyperplasia has not been evaluated in patients with hepatic insufficiency. If Tadalafil Lilly is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis

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.

Tadalafil Lilly, 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).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing Tadalafil Lilly to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

Tadalafil Lilly and other treatments for erectile dysfunction

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

Lactose

Tadalafil Lilly contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

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

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

Cytochrome P450 inhibitors
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 adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of medicinal product interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
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

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical trial 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 Tadalafil Lilly

(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 Tadalafil Lilly before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).

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

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

Riociguat
Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor

and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
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 maximise 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).

Cytochrome P450 metabolised medicinal products
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.

CYP2C9 substrates (e.g. R-warfarin)
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.

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

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

Tadalafil Lilly is not indicated for use by women.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tadalafil Lilly during pregnancy.

Breast-feeding

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

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking Tadalafil Lilly for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadalafil Lilly. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadalafil Lilly once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 8 022 patients on Tadalafil Lilly and 4 422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

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

System organ class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity reactions	Angioedema[2]	
Nervous system disorders		Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia	

Eye disorders			Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]	Central serous chorioretinopathy
Ear and labyrinth disorders			Tinnitus	Sudden hearing loss	
Cardiac disorders[1]			Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]	
Vascular disorders		Flushing	Hypotension[3], Hypertension		
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea, Epistaxis		
Gastrointestinal disorders		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux		
Skin and subcutaneous tissue disorders			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)	
Musculoskeletal, connective tissue and bone disorders		Back pain, Myalgia, Pain in extremity			
Renal and urinary disorders			Haematuria		
Reproductive system and breast disorders			Prolonged erections	Priapism, Penile haemorrhage, Haematospermia	
General disorders and administration site conditions			Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1, 2]	

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).

(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

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

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

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

Erectile dysfunction
For Tadalafil Lilly on demand, three clinical studies were conducted in 1 054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

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

For once-a-day evaluation of tadalafil at doses of 2.5, 5, and 10 mg 3 clinical studies were initially conducted involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, the mean per-subject proportion of successful intercourse attempts were 57 and 67 % on Tadalafil Lilly 5 mg, 50 % on Tadalafil Lilly 2.5 mg as compared to 31 and 37 % with placebo. In the study in patients with erectile dysfunction secondary to diabetes, the mean per-subject proportion of successful attempts were 41 and 46 % on Tadalafil Lilly 5 mg and 2.5 mg, respectively, as compared to 28 % with placebo. Most patients in these three studies were responders to previous on-demand treatment with PDE5 inhibitors. In a subsequent study, 217 patients who were treatment-naïve to PDE5 inhibitors were randomised to Tadalafil Lilly 5 mg once a day vs. placebo. The mean per-subject proportion of successful sexual intercourse attempts was 68 % for Tadalafil Lilly patients compared to 52 % for patients on placebo.

Benign prostatic hyperplasia
Tadalafil Lilly was studied in 4 clinical studies of 12 weeks duration enrolling over 1 500 patients with signs and symptoms of benign prostatic hyperplasia. The improvement in the total international prostate symptom score with Tadalafil Lilly 5 mg in the four studies were -4.8, -5.6, -6.1 and -6.3 compared to -2.2, -3.6, -3.8 and -4.2 with placebo. The improvements in total international prostate symptom score occurred as early as 1 week. In one of the studies, which also included tamsulosin 0.4 mg as an active comparator, the improvement in total international prostate symptom score with Tadalafil Lilly 5 mg, tamsulosin and placebo were -6.3, -5.7 and -4.2 respectively.

One of these studies assessed improvements in erectile dysfunction and signs and symptoms of benign prostatic hyperplasia in patients with both conditions. The improvements in the erectile function domain of the international index of erectile function and the total international prostate symptom score in this study were 6.5 and -6.1 with Tadalafil Lilly 5 mg compared to 1.8 and -3.8 with placebo, respectively. The mean per-subject proportion of successful sexual intercourse attempts was 71.9% with Tadalafil Lilly 5 mg compared to 48.3% with placebo.

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

Paediatric population

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

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 Tadalafil Lilly 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 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of Tadalafil Lilly 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 Tadalafil Lilly 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 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance 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 blisters in cartons of 14, 28 or 84 film-coated tablets.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/002
EU/1/17/1177/003
EU/1/17/1177/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017
Date of latest renewal: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 10 mg film-coated tablets
Tadalafil Lilly 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tadalafil Lilly 10 mg film-coated tablets

Each tablet contains 10 mg tadalafil.

Excipient with known effect
Each coated tablet contains 170 mg lactose (as monohydrate).

Tadalafil Lilly 20 mg film-coated tablets

Each tablet contains 20 mg tadalafil.

Excipient with known effect
Each coated tablet contains 233 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Tadalafil Lilly 10 mg film-coated tablets

Light yellow and almond shaped tablets of 10.81 mm by 6.59 mm, marked "C 10" on one side.

Tadalafil Lilly 20 mg film-coated tablets

Yellow and almond shaped tablets of 12.09 mm by 7.37 mm, marked "C 20" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

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

Tadalafil Lilly is not indicated for use by women.

4.2 Posology and method of administration

Posology

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 patients who anticipate a frequent use of Tadalafil Lilly (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil Lilly 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.

Special populations

Elderly men
Dose adjustments are not required in elderly patients.

Men with renal impairment
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).

Men with hepatic impairment
The recommended dose of Tadalafil Lilly is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil Lilly 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 sections 4.4 and 5.2).

Men with diabetes
Dose adjustments are not required in diabetic patients.

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

Method of administration

Oral use.

Tadalafil Lilly is available as 2.5, 5, 10, and 20 mg film-coated tablets.

The tablets should be swallowed whole with water, with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

Tadalafil Lilly, 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.

Tadalafil Lilly is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous Phosphodiesterase-5 (PDE5) inhibitor exposure (see section 4.4).

The co-administration of PDE5 inhibitors, including tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with Tadalafil Lilly

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 potentiates the hypotensive effect of nitrates (see section 4.3).

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 Tadalafil Lilly is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular

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 Tadalafil Lilly, to sexual activity, or to a combination of these or other factors.

In patients who are taking alpha$_1$ blockers, concomitant administration of Tadalafil Lilly may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of Tadalafil Lilly and other PDE5 inhibitors. Most cases of

CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, he should stop taking Tadalafil Lilly and consult a physician immediately (see section 4.3).

Decreased or sudden hearing loss

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

Hepatic impairment

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

Priapism and anatomical deformation of the penis

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.

Tadalafil Lilly, 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).

Use with CYP3A4 inhibitors

Caution should be exercised when prescribing Tadalafil Lilly to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin) as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

Tadalafil Lilly and other treatments for erectile dysfunction

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

Lactose

Tadalafil Lilly contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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

Cytochrome P450 inhibitors
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 adverse reactions listed in section 4.8 might be increased.

Transporters
The role of transporters (for example p-glycoprotein) in the disposition of tadalafil is not known. Therefore there is the potential of medicinal product interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
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

Nitrates
In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil Lilly to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical trial 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 Tadalafil Lilly (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 Tadalafil Lilly before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)
The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore this combination is not recommended (see section 4.4).
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However, caution should be exercised when using tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dose and progressively adjusted.

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10 mg except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical

pharmacology study tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood-pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha blockers -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat
Preclinical studies showed an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

5- alpha reductase inhibitors
In a clinical trial that compared tadalafil 5 mg coadministered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
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 maximise 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).

Cytochrome P450 metabolised medicinal products
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.

CYP2C9 substrates (e.g. R-warfarin)
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.

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

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

Tadalafil Lilly is not indicated for use by women.

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tadalafil Lilly during pregnancy.

Breast-feeding

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

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking Tadalafil Lilly for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of Tadalafil Lilly. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Tadalafil Lilly once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 8 022 patients on Tadalafil Lilly and

4 422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

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

System organ class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity reactions	Angioedema[2]	
Nervous system disorders		Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia	
Eye disorders			Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION) [2], Retinal vascular occlusion[2]	Central serous chorioretinopathy
Ear and labyrinth disorders			Tinnitus	Sudden hearing loss	
Cardiac disorders[1]			Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular arrhythmia[2]	
Vascular disorders		Flushing	Hypotension[3], Hypertension		
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Dyspnoea, Epistaxis		

Gastrointestinal disorders		Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux		
Skin and subcutaneous tissue disorders			Rash	Urticaria, Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)	
Musculoskeletal, connective tissue and bone disorders		Back pain, Myalgia, Pain in extremity			
Renal and urinary disorders			Haematuria		
Reproductive system and breast disorders			Prolonged erections	Priapism, Penile haemorrhage, Haematospermia	
General disorders and administration site conditions			Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac death[1,2]	

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4, enzymes which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10 000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Three clinical studies were conducted in 1 054 patients in an at-home setting to define the period of responsiveness to Tadalafil Lilly. 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 Tadalafil Lilly 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 3 250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81 % of patients reported that Tadalafil Lilly improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking Tadalafil Lilly (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 Tadalafil Lilly 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.

Paediatric population

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction. See section 4.2 for information on paediatric use.

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 Tadalafil Lilly 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 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Hepatic insufficiency
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of Tadalafil Lilly in patients with severe hepatic insufficiency (Child-Pugh Class C). If Tadalafil Lilly 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 1 000 mg/kg/day tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free active substance 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
Coscarmellose 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

Tadalafil Lilly 10 mg film-coated tablets

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

Tadalafil Lilly 20 mg film-coated tablets

Aluminium/PVC 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

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

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/005
EU/1/17/1177/006
EU/1/17/1177/007
EU/1/17/1177/008
EU/1/17/1177/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017
Date of latest renewal: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 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

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily.
Read the package leaflet before use.
For oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tadalafil lilly 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 2.5 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 5 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg tadalafil

3. LIST OF EXCIPIENTS

lactose

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

14 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily.
Read the package leaflet before use.
For oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/002-004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tadalafil lilly 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 5 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 10 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg tadalafil

3. LIST OF EXCIPIENTS

lactose

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

4 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tadalafil lilly 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 10 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 20 mg film-coated tablets
tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg tadalafil

3. LIST OF EXCIPIENTS

lactose

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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.
Orteliuslaan 1000, 3528 BD Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1177/006-009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tadalafil lilly 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Tadalafil Lilly 20 mg tablets
tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tadalafil Lilly 2.5 mg film-coated tablets
tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tadalafil Lilly is and what it is used for
2. What you need to know before you take Tadalafil Lilly
3. How to take Tadalafil Lilly
4. Possible side effects
5 How to store Tadalafil Lilly
6. Contents of the pack and other information

1. What Tadalafil Lilly is and what it is used for

Tadalafil Lilly is a treatment for adult men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity. Tadalafil Lilly has been shown to significantly improve the ability of obtaining a hard erect penis suitable for sexual activity.

Tadalafil Lilly contains the active substance tadalafil which belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation Tadalafil Lilly 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. Tadalafil Lilly will not help you if you do not have erectile dysfunction.

It is important to note that Tadalafil Lilly 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. What you need to know before you take Tadalafil Lilly

Do not take Tadalafil Lilly if you:
- are allergic to tadalafil or any of the other ingredients of this medicine (listed in section 6).
- 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”). Tadalafil Lilly has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- have serious heart disease or recently had a heart attack within the last 90 days.
- recently had a stroke within the last 6 months.
- have low blood pressure or uncontrolled high blood pressure.
- ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.
- are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). Phosphodiesterase-5 (PDE5) inhibitors, such as Tadalafil Lilly, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions
Talk to your doctor before taking Tadalafil Lilly.

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.

Before taking the tablets, tell your doctor if you have:
- sickle cell anaemia (an abnormality of red blood cells).
- multiple myeloma (cancer of the bone marrow).
- leukaemia (cancer of the blood cells).
- any deformation of your penis.
- a serious liver problem.
- a severe kidney problem.

It is not known if Tadalafil Lilly is effective in patients who have had:
- pelvic surgery.
- removal of all or part of the prostate gland in which nerves of the prostate are cut (radical non-nerve-sparing prostatectomy).

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking Tadalafil Lilly, stop taking Tadalafil Lilly and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, stop taking Tadalafil Lilly and contact your doctor immediately.

Tadalafil Lilly is not intended for use by women.

Children and adolescents
Tadalafil Lilly is not intended for use by children and adolescents under the age of 18.

Other medicines and Tadalafil Lilly
Tell your doctor if you are taking, have recently taken or might take any other medicines

Do not take Tadalafil Lilly if you are already taking nitrates.

Some medicines may be affected by Tadalafil Lilly or they may affect how well Tadalafil Lilly will work. Tell your doctor or pharmacist if you are already taking:

- an alpha blocker (used to treat high blood pressure or urinary symptoms due to a condition where prostate gland enlarges in men).
- other medicines to treat high blood pressure.
- riociguat.
- a 5-alpha reductase inhibitor (used to treat benign prostatic hyperplasia).
- medicines such as ketoconazole or itraconazole (to treat fungal infections) and protease inhibitors for treatment of AIDS or HIV infection.
- erythromycin or clarithromycin (antibiotic to treat bacterial infection)
- phenobarbital, phenytoin and carbamazepine (anticonvulsant medicines).
- rifampicin (antibiotic to treat mycobacterial infection).
- other treatments for erectile dysfunction.

Tadalafil Lilly with drink and alcohol
Information on the effect of alcohol is in section 3. Grapefruit juice may affect how well Tadalafil Lilly will work and should be taken with caution. Talk to your doctor for further information.

Fertility
When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines
Some men taking Tadalafil Lilly in clinical studies have reported dizziness. Check carefully how you react to the tablets before driving or using machines.

Tadalafil Lilly contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Tadalafil Lilly

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Tadalafil Lilly tablets are for oral use in men only. Swallow the tablet whole with some water. The tablets can be taken with or without food.

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 Tadalafil Lilly. This will be given as a 2.5 mg tablet.
Do not take Tadalafil Lilly more than once a day.

Once a day dosing of Tadalafil Lilly may be useful to men who anticipate having sexual activity two or more times per week.

When taken once a day Tadalafil Lilly 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 Tadalafil Lilly 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 and may temporarily lower your blood pressure. If you have taken or are planning to take Tadalafil Lilly, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.

If you take more Tadalafil Lilly than you should
Contact your doctor. You may experience side effects described in section 4.

If you forget to take Tadalafil Lilly
Take your dose as soon as you remember but do not take a double dose to make up for a forgotten tablet. You should not take Tadalafil Lilly more than once a day.

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

4. Possible side effects

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

If you experience any of the following side effects stop taking the medicine and seek medical help immediately:
- allergic reactions including rashes (frequency uncommon).
- chest pain - do not use nitrates but seek immediate medical assistance (frequency uncommon).
- priapism, a prolonged and possibly painful erection after taking Tadalafil Lilly (frequency rare). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
- sudden loss of vision (frequency rare), distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

Other side effects have been reported:

Common (may affect up to 1 in 10 people)
- headache, back pain, muscle aches, pain in arms and legs, facial flushing, nasal congestion and indigestion.

Uncommon (may affect up to 1 in 100 people)
- dizziness, stomach ache, feeling sick, being sick (vomiting), reflux, blurred vision, eye pain, difficulty in breathing, presence of blood in urine, prolonged erection, pounding heartbeat sensation, a fast heart rate, high blood pressure, low blood pressure, nose bleeds, ringing in the ears, swelling of the hands, feet or ankles and feeling tired.

Rare (may affect up to 1 in 1 000 people)
- fainting, seizures and passing memory loss, swelling of the eyelids, red eyes, sudden decrease or loss of hearing, hives (itchy red welts on the surface of the skin), penile bleeding, presence of blood in semen and increased sweating.

Heart attack and stroke have also been reported rarely in men taking Tadalafil Lilly. Most of these men had known heart problems before taking this medicine.

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

Some additional rare side effects have been reported in men taking Tadalafil Lilly that were not seen in clinical trials. These include:
- migraine, swelling of the face, serious allergic reaction which causes swelling of the face or throat, serious skin rashes, some disorders affecting blood flow to the eyes, irregular heartbeats, angina and sudden cardiac death.
- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The side effect dizziness has been reported more frequently in men over 75 years of age taking Tadalafil Lilly. Diarrhoea has been reported more frequently in men over 65 years of age taking Tadalafil Lilly.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tadalafil Lilly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tadalafil Lilly 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. See section 2 "Tadalafil Lilly contains lactose".
  Film-coat: Lactose monohydrate, Hypromellose, Triacetin, Titanium dioxide (E171), Iron oxide yellow (E172), Iron oxide red (E172), Talc.

What Tadalafil Lilly looks like and contents of the pack
Tadalafil Lilly 2.5 mg is a light orange-yellow film-coated tablet in the shape of an almond and has "C 2 ½" marked on one side. The tablet is 8.58 mm by 5.23 mm.

Tadalafil Lilly 2.5 mg is available in blister packs containing 28 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the user

Tadalafil Lilly 5 mg film-coated tablets
tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tadalafil Lilly is and what it is used for
2. What you need to know before you take Tadalafil Lilly
3. How to take Tadalafil Lilly
4. Possible side effects
5 How to store Tadalafil Lilly
6. Contents of the pack and other information

1. What Tadalafil Lilly is and what it is used for
Tadalafil Lilly contains the active substance tadalafil which belongs to a group of medicines called phosphodiesterase type 5 inhibitors.

Tadalafil Lilly 5 mg is used to treat adult men with:
- **erectile dysfunction**. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity. Tadalafil Lilly has been shown to significantly improve the ability of obtaining a hard erect penis suitable for sexual activity.
  Following sexual stimulation Tadalafil Lilly 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. Tadalafil Lilly will not help you if you do not have erectile dysfunction. It is important to note that Tadalafil Lilly for the treatment of erectile dysfunction 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.

- urinary symptoms associated with a common condition called **benign prostatic hyperplasia**. This is when the prostate gland gets bigger with age. Symptoms include difficulty in starting to pass water, a feeling of not completely emptying the bladder and a more frequent need to pass water even at night. Tadalafil Lilly improves blood flow to, and relaxes the muscles of, the prostate and bladder which may reduce symptoms of benign prostatic hyperplasia. Tadalafil Lilly has been shown to improve these urinary symptoms as early as 1-2 weeks after starting treatment.

2. What you need to know before you take Tadalafil Lilly

Do not take Tadalafil Lilly if you:
- are allergic to tadalafil or any of the other ingredients of this medicine (listed in section 6).
- 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”). Tadalafil Lilly has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- have serious heart disease or recently had a heart attack within the last 90 days.
- recently had a stroke within the last 6 months.

- have low blood pressure or uncontrolled high blood pressure.
- ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.
- are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). Phosphodiesterase-5 (PDE5) inhibitors, such as Tadalafil Lilly, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions
Talk to your doctor before taking Tadalafil Lilly.

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.

Since benign prostatic hyperplasia and prostate cancer may have the same symptoms, your doctor will check you for prostate cancer before starting treatment with Tadalafil Lilly for benign prostatic hyperplasia. Tadalafil Lilly does not treat prostate cancer.

Before taking the tablets, tell your doctor if you have:
- sickle cell anaemia (an abnormality of red blood cells).
- multiple myeloma (cancer of the bone marrow).
- leukaemia (cancer of the blood cells).
- any deformation of your penis.
- a serious liver problem.
- a severe kidney problem.

It is not known if Tadalafil Lilly is effective in patients who have had:
- pelvic surgery.
- removal of all or part of the prostate gland in which nerves of the prostate are cut (radical non-nerve-sparing prostatectomy).

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking Tadalafil Lilly, stop taking Tadalafil Lilly and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, stop taking Tadalafil Lilly and contact your doctor immediately.

Tadalafil Lilly is not intended for use by women.

Children and adolescents
Tadalafil Lilly is not intended for use by children and adolescents under the age of 18.

Other medicines and Tadalafil Lilly
Tell your doctor if you are taking, have recently taken or might take any other medicines

Do not take Tadalafil Lilly if you are already taking nitrates.

Some medicines may be affected by Tadalafil Lilly or they may affect how well Tadalafil Lilly will work. Tell your doctor or pharmacist if you are already taking:

- an alpha blocker (used to treat high blood pressure or urinary symptoms due to a condition where prostate gland enlarges in men).
- other medicines to treat high blood pressure.
- riociguat.
- a 5-alpha reductase inhibitor (used to treat benign prostatic hyperplasia).

- medicines such as ketoconazole or itraconazole (to treat fungal infections) and protease inhibitors for treatment of AIDS or HIV infection.
- erythromycin or clarithromycin (antibiotic to treat bacterial infection).
- phenobarbital, phenytoin and carbamazepine (anticonvulsant medicines).
- rifampicin (antibiotic to treat mycobacterial infection).
- other treatments for erectile dysfunction.

Tadalafil Lilly with drink and alcohol
Information on the effect of alcohol is in section 3. Grapefruit juice may affect how well Tadalafil Lilly will work and should be taken with caution. Talk to your doctor for further information.

Fertility
When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines
Some men taking Tadalafil Lilly in clinical studies have reported dizziness. Check carefully how you react to the tablets before driving or using machines.

Tadalafil Lilly contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Tadalafil Lilly

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Tadalafil Lilly tablets are for oral use in men only. Swallow the tablet whole with some water. The tablets can be taken with or without food.

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

For the treatment of erectile dysfunction
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 Tadalafil Lilly. This will be given as a 2.5 mg tablet.
Do not take Tadalafil Lilly more than once a day.

When taken once a day Tadalafil Lilly allows you to obtain an erection, when sexually stimulated, at any time point during the 24 hours of the day. Once a day dosing of Tadalafil Lilly may be useful to men who anticipate having sexual activity two or more times per week.
It is important to note that Tadalafil Lilly 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.

For the treatment benign prostatic hyperplasia
The **dose** is one 5 mg tablet taken once a day at approximately the same time of the day.
If you have benign prostatic hyperplasia and erectile dysfunction, the dose remains one 5 mg tablet taken once a day.
Do not take Tadalafil Lilly more than once a day.

If you take more Tadalafil Lilly than you should
Contact your doctor. You may experience side effects described in section 4.

If you forget to take Tadalafil Lilly
Take your dose as soon as you remember but do not take a double dose to make up for a forgotten tablet. You should not take Tadalafil Lilly more than once a day.

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

4. Possible side effects

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

If you experience any of the following side effects stop taking the medicine and seek medical help immediately:
- allergic reactions including rashes (frequency uncommon).
- chest pain - do not use nitrates but seek immediate medical assistance (frequency uncommon).
- priapism, a prolonged and possibly painful erection after taking Tadalafil Lilly (frequency rare). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
- sudden loss of vision (frequency rare), distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

Other side effects have been reported:

Common (may affect up to 1 in 10 people)
- headache, back pain, muscle aches, pain in arms and legs, facial flushing, nasal congestion and indigestion.

Uncommon (may affect up to 1 in 100 people)
- dizziness, stomach ache, feeling sick, being sick (vomiting), reflux, blurred vision, eye pain, difficulty in breathing, presence of blood in urine, prolonged erection, pounding heartbeat sensation, a fast heart rate, high blood pressure, low blood pressure, nose bleeds, ringing in the ears, swelling of the hands, feet or ankles and feeling tired.

Rare (may affect up to 1 in 1 000 people)
- fainting, seizures and passing memory loss, swelling of the eyelids, red eyes, sudden decrease or loss of hearing, hives (itchy red welts on the surface of the skin), penile bleeding, presence of blood in semen and increased sweating.

Heart attack and stroke have also been reported rarely in men taking Tadalafil Lilly. Most of these men had known heart problems before taking this medicine.

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

Some additional rare side effects have been reported in men taking Tadalafil Lilly that were not seen in clinical trials. These include:
- migraine, swelling of the face, serious allergic reaction which causes swelling of the face or throat, serious skin rashes, some disorders affecting blood flow to the eyes, irregular heartbeats, angina and sudden cardiac death.
- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The side effect dizziness has been reported more frequently in men over 75 years of age taking Tadalafil Lilly. Diarrhoea has been reported more frequently in men over 65 years of age taking Tadalafil Lilly.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tadalafil Lilly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tadalafil Lilly 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. See section 2 "Tadalafil Lilly contains lactose".
  Film-coat: Lactose monohydrate, Hypromellose, Triacetin, Titanium dioxide (E171), Iron oxide yellow (E172), Talc.

What Tadalafil Lilly looks like and contents of the pack
Tadalafil Lilly 5 mg is a light yellow film-coated tablet in the shape of an almond and has "C 5" marked on one side. The tablet is 9.59 mm by 5.85 mm.

Tadalafil Lilly 5 mg is available in blister packs containing 14, 28 or 84 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the user

Tadalafil Lilly 10 mg film-coated tablets
tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tadalafil Lilly is and what it is used for
2. What you need to know before you take Tadalafil Lilly
3. How to take Tadalafil Lilly
4. Possible side effects
5 How to store Tadalafil Lilly
6. Contents of the pack and other information

1. What Tadalafil Lilly is and what it is used for

Tadalafil Lilly is a treatment for adult men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity. Tadalafil Lilly has been shown to significantly improve the ability of obtaining a hard erect penis suitable for sexual activity.

Tadalafil Lilly contains the active substance tadalafil which belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation Tadalafil Lilly 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. Tadalafil Lilly will not help you if you do not have erectile dysfunction.

It is important to note that Tadalafil Lilly 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. What you need to know before you take Tadalafil Lilly

Do not take Tadalafil Lilly if you:
- are allergic to tadalafil or any of the other ingredients of this medicine (listed in section 6).
- 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”). Tadalafil Lilly has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- have serious heart disease or recently had a heart attack within the last 90 days.
- recently had a stroke within the last 6 months.
- have low blood pressure or uncontrolled high blood pressure.
- ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.
- are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). Phosphodiesterase-5 (PDE5) inhibitors, such as Tadalafil Lilly, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions
Talk to your doctor before taking Tadalafil Lilly.

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.

Before taking the tablets, tell your doctor if you have:
- sickle cell anaemia (an abnormality of red blood cells).
- multiple myeloma (cancer of the bone marrow).
- leukaemia (cancer of the blood cells).
- any deformation of your penis.
- a serious liver problem.
- a severe kidney problem.

It is not known if Tadalafil Lilly is effective in patients who have had:
- pelvic surgery.
- removal of all or part of the prostate gland in which nerves of the prostate are cut (radical non-nerve-sparing prostatectomy).

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking Tadalafil Lilly, stop taking Tadalafil Lilly and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, stop taking Tadalafil Lilly and contact your doctor immediately.

Tadalafil Lilly is not intended for use by women.

Children and adolescents
Tadalafil Lilly is not intended for use by children and adolescents under the age of 18.

Other medicines and Tadalafil Lilly
Tell your doctor if you are taking, have recently taken or might take any other medicines

Do not take Tadalafil Lilly if you are already taking nitrates.

Some medicines may be affected by Tadalafil Lilly or they may affect how well Tadalafil Lilly will work. Tell your doctor or pharmacist if you are already taking:

- an alpha blocker (used to treat high blood pressure or urinary symptoms due to a condition where prostate gland enlarges in men).
- other medicines to treat high blood pressure.
- riociguat.
- a 5-alpha reductase inhibitor (used to treat benign prostatic hyperplasia).
- medicines such as ketoconazole or itraconazole(to treat fungal infections) and protease inhibitors for treatment of AIDS or HIV infection.
- erythromycin or clarithromycin (antibiotic to treat bacterial infection)
- phenobarbital, phenytoin and carbamazepine (anticonvulsant medicines).
- rifampicin (antibiotic to treat mycobacterial infection).
- other treatments for erectile dysfunction.

Tadalafil Lilly with drink and alcohol
Information on the effect of alcohol is in section 3. Grapefruit juice may affect how well Tadalafil Lilly will work and should be taken with caution. Talk to your doctor for further information.

Fertility
When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines
Some men taking Tadalafil Lilly in clinical studies have reported dizziness. Check carefully how you react to the tablets before driving or using machines.

Tadalafil Lilly contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Tadalafil Lilly

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Tadalafil Lilly tablets are for oral use in men only. Swallow the tablet whole with some water. The tablets can be taken with or without food.

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. Tadalafil Lilly tablets are for oral use.

You may take a Tadalafil Lilly tablet at least 30 minutes before sexual activity.
Tadalafil Lilly may still be effective up to 36 hours after taking the tablet.

Do not take Tadalafil Lilly more than once a day. Tadalafil Lilly 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not recommended for continuous daily use.

It is important to note that Tadalafil Lilly 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 and may temporarily lower your blood pressure. If you have taken or are planning to take Tadalafil Lilly, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.

If you take more Tadalafil Lilly than you should
Contact your doctor. You may experience side effects described in section 4.

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

4. Possible side effects

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

If you experience any of the following side effects stop taking the medicine and seek medical help immediately:
- allergic reactions including rashes (frequency uncommon).
- chest pain - do not use nitrates but seek immediate medical assistance (frequency uncommon).

- priapism, a prolonged and possibly painful erection after taking Tadalafil Lilly (frequency rare). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
- sudden loss of vision (frequency rare), distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

Other side effects have been reported:

Common (may affect up to 1 in 10 people)
- headache, back pain, muscle aches, pain in arms and legs, facial flushing, nasal congestion and indigestion.

Uncommon (may affect up to 1 in 100 people)
- dizziness, stomach ache, feeling sick, being sick (vomiting), reflux, blurred vision, eye pain, difficulty in breathing, presence of blood in urine, prolonged erection, pounding heartbeat sensation, a fast heart rate, high blood pressure, low blood pressure, nose bleeds, ringing in the ears, swelling of the hands, feet or ankles and feeling tired.

Rare (may affect up to 1 in 1 000 people)
- fainting, seizures and passing memory loss, swelling of the eyelids, red eyes, sudden decrease or loss of hearing, hives (itchy red welts on the surface of the skin), penile bleeding, presence of blood in semen and increased sweating.

Heart attack and stroke have also been reported rarely in men taking Tadalafil Lilly. Most of these men had known heart problems before taking this medicine.

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

Some additional rare side effects have been reported in men taking Tadalafil Lilly that were not seen in clinical trials. These include:
- migraine, swelling of the face, serious allergic reaction which causes swelling of the face or throat, serious skin rashes, some disorders affecting blood flow to the eyes, irregular heartbeats, angina and sudden cardiac death.
- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The side effect dizziness has been reported more frequently in men over 75 years of age taking Tadalafil Lilly. Diarrhoea has been reported more frequently in men over 65 years of age taking Tadalafil Lilly.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tadalafil Lilly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tadalafil Lilly 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. See section 2 “Tadalafil Lilly contains lactose”.
  Film-coat: Lactose monohydrate, Hypromellose, Triacetin, Titanium dioxide (E171), Iron oxide yellow (E172), Talc.

What Tadalafil Lilly looks like and contents of the pack

Tadalafil Lilly 10 mg is a light yellow film-coated tablet in the shape of an almond and has "C 10" marked on one side. The tablet is 10.81 mm by 6.59 mm.

Tadalafil Lilly 10 mg is available in blister packs containing 4 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Package leaflet: Information for the user

Tadalafil Lilly 20 mg film-coated tablets
tadalafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tadalafil Lilly is and what it is used for
2. What you need to know before you take Tadalafil Lilly
3. How to take Tadalafil Lilly
4. Possible side effects
5 How to store Tadalafil Lilly
6. Contents of the pack and other information

1. What Tadalafil Lilly is and what it is used for

Tadalafil Lilly is a treatment for adult men with erectile dysfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity. Tadalafil Lilly has been shown to significantly improve the ability of obtaining a hard erect penis suitable for sexual activity.

Tadalafil Lilly contains the active substance tadalafil which belongs to a group of medicines called phosphodiesterase type 5 inhibitors. Following sexual stimulation Tadalafil Lilly 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. Tadalafil Lilly will not help you if you do not have erectile dysfunction.

It is important to note that Tadalafil Lilly 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. What you need to know before you take Tadalafil Lilly

Do not take Tadalafil Lilly if you:
- are allergic to tadalafil or any of the other ingredients of this medicine (listed in section 6).
- 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”). Tadalafil Lilly has been shown to increase the effects of these medicines. If you are taking any form of nitrate or are unsure tell your doctor.
- have serious heart disease or recently had a heart attack within the last 90 days.
- recently had a stroke within the last 6 months.
- have low blood pressure or uncontrolled high blood pressure.
- ever had loss of vision because of non-arteritic anterior ischemic optic neuropathy (NAION), a condition described as “stroke of the eye”.
- are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). Phosphodiesterase-5 (PDE5) inhibitors, such as Tadalafil Lilly, have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Warnings and precautions
Talk to your doctor before taking Tadalafil Lilly.

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.

Before taking the tablets, tell your doctor if you have:
- sickle cell anaemia (an abnormality of red blood cells).
- multiple myeloma (cancer of the bone marrow).
- leukaemia (cancer of the blood cells).
- any deformation of your penis.
- a serious liver problem.
- a severe kidney problem.

It is not known if Tadalafil Lilly is effective in patients who have had:
- pelvic surgery.
- removal of all or part of the prostate gland in which nerves of the prostate are cut (radical non-nerve-sparing prostatectomy).

If you experience sudden decrease or loss of vision or your vision is distorted, dimmed while you are taking Tadalafil Lilly, stop taking Tadalafil Lilly and contact your doctor immediately.

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, stop taking Tadalafil Lilly and contact your doctor immediately.

Tadalafil Lilly is not intended for use by women.

Children and adolescents
Tadalafil Lilly is not intended for use by children and adolescents under the age of 18.

Other medicines and Tadalafil Lilly
Tell your doctor if you are taking, have recently taken or might take any other medicines

Do not take Tadalafil Lilly if you are already taking nitrates.

Some medicines may be affected by Tadalafil Lilly or they may affect how well Tadalafil Lilly will work. Tell your doctor or pharmacist if you are already taking:

- an alpha blocker (used to treat high blood pressure or urinary symptoms due to a condition where prostate gland enlarges in men).
- other medicines to treat high blood pressure.
- riociguat.
- a 5- alpha reductase inhibitor (used to treat benign prostatic hyperplasia).
- medicines such as ketoconazole or itraconazole (to treat fungal infections) and protease inhibitors for treatment of AIDS or HIV infection.
- erythromycin or clarithromycin (antibiotic to treat bacterial infection)
- phenobarbital, phenytoin and carbamazepine (anticonvulsant medicines).
- rifampicin (antibiotic to treat mycobacterial infection).
- other treatments for erectile dysfunction.

Tadalafil Lilly with drink and alcohol
Information on the effect of alcohol is in section 3. Grapefruit juice may affect how well Tadalafil Lilly will work and should be taken with caution. Talk to your doctor for further information.

Fertility
When dogs were treated there was reduced sperm development in the testes. A reduction in sperm was seen in some men. These effects are unlikely to lead to a lack of fertility.

Driving and using machines
Some men taking Tadalafil Lilly in clinical studies have reported dizziness. Check carefully how you react to the tablets before driving or using machines.

Tadalafil Lilly contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Tadalafil Lilly

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Tadalafil Lilly tablets are for oral use in men only. Swallow the tablet whole with some water. The tablets can be taken with or without food.

The recommended starting dose is one 10 mg tablet before sexual activity. However, you have been given the dose of one 20 mg tablet as your doctor has decided that the recommended dose of 10 mg is too weak.

You may take a Tadalafil Lilly tablet at least 30 minutes before sexual activity.
Tadalafil Lilly may still be effective up to 36 hours after taking the tablet.

Do not take Tadalafil Lilly more than once a day. Tadalafil Lilly 10 mg and 20 mg is intended for use prior to anticipated sexual activity and is not recommended for continuous daily use.

It is important to note that Tadalafil Lilly 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 and may temporarily lower your blood pressure. If you have taken or are planning to take Tadalafil Lilly, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.

If you take more Tadalafil Lilly than you should
Contact your doctor. You may experience side effects described in section 4.

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

4. Possible side effects

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

If you experience any of the following side effects stop taking the medicine and seek medical help immediately:
- allergic reactions including rashes (frequency uncommon).
- chest pain - do not use nitrates but seek immediate medical assistance (frequency uncommon).
- priapism, a prolonged and possibly painful erection after taking Tadalafil Lilly (frequency rare). If you have such an erection, which lasts continuously for more than 4 hours you should contact a doctor immediately.
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Other side effects have been reported:

Common (may affect up to 1 in 10 people)
- headache, back pain, muscle aches, pain in arms and legs, facial flushing, nasal congestion and indigestion.

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Rare (may affect up to 1 in 1 000 people)
- fainting, seizures and passing memory loss, swelling of the eyelids, red eyes, sudden decrease or loss of hearing, hives (itchy red welts on the surface of the skin), penile bleeding, presence of blood in semen and increased sweating.

Heart attack and stroke have also been reported rarely in men taking Tadalafil Lilly. Most of these men had known heart problems before taking this medicine.

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

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- distorted, dimmed, blurred central vision or sudden decrease of vision (frequency not known).

The side effect dizziness has been reported more frequently in men over 75 years of age taking Tadalafil Lilly. Diarrhoea has been reported more frequently in men over 65 years of age taking Tadalafil Lilly.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tadalafil Lilly

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tadalafil Lilly 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. See section 2 “Tadalafil Lilly contains lactose”.
  Film-coat: Lactose monohydrate, Hypromellose, Triacetin, Titanium dioxide (E171), Iron oxide yellow (E172), Talc.

What Tadalafil Lilly looks like and contents of the pack
Tadalafil Lilly 20 mg is a yellow film-coated tablet in the shape of an almond and has "C 20" marked on one side. The tablet is 12.09 mm by 7.37 mm.

Tadalafil Lilly 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

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Orteliuslaan 1000, 3528 BD Utrecht, The Netherlands.

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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