Attachment 1a

CIALIS®

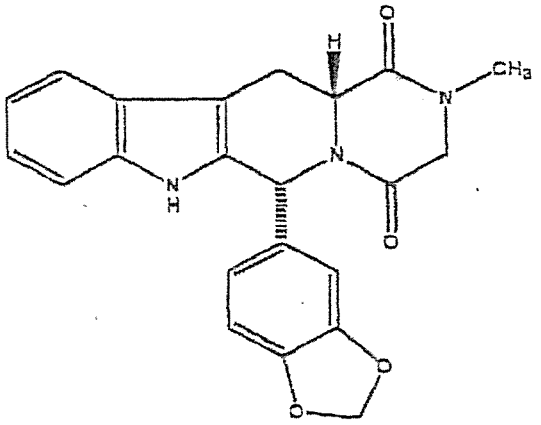
(tadalafil)

NAME

CIALIS® (tadalafil).

Chemically, tadalafil is pyrazino[1', 2':1, 6]pyrido[3, 4-b]indole-1, 4-dione, 6-(1, 3-benzodioxol-5-yl)-2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-, (6R, 12aR)-. Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. Tadalafil is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol. The CAS number for tadalafil is 171596-29-5.

Tadalafil has the following structural formula:



DESCRIPTION

CIALIS 20 mg tablets are yellow, film coated, almond shaped tablets for oral administration, marked "C 20" on one side. CIALIS 10 mg tablets are light yellow, film coated, almond shaped tablets for oral administration, marked "C 10" on one side. Each tablet contains 20 mg or 10 mg, respectively, of tadalafil and the following excipients: croscarmellose sodium, hydroxypropylcellulose, hypromellose, iron oxide yellow CI77492, lactose, magnesium stearate, cellulose - microcrystalline, sodium lauryl sulfate, talc - purified, titanium dioxide and glycerol triacetate.

PHARMACOLOGY

Pharmacodynamics

Tadalafil is a reversible inhibitor of cyclic guanosine monophosphate (cGMP) – specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric

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side, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that tadalafil inhibits PDE5 more potently than other PDEs. PDE5 is an enzyme found in the corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung and cerebellum. 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 >9,000-fold more potent for PDE5 than for PDE7 through PDE10.

Studies of CIALIS on vision – In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (see ADVERSE REACTIONS).

Studies of CIALIS on blood pressure and heart rate –Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively) and no significant change in heart rate. Larger effects were recorded among subjects receiving concomitant nitrates (see CONTRAINDICATIONS). When tadalafil and certain oral antihypertensive medications were assessed in drug interaction studies, tadalafil did not result in clinically significant augmentation of the antihypertensive effects of those medications (see PRECAUTIONS – Interactions with Other Drugs).

Pharmacokinetics

Absorption – Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. There is no clinically relevant effect of food on the rate and extent of absorption of tadalafil, thus tadalafil may be taken with or without food. The time of dosing (morning versus evening) has no clinically relevant effects on the rate and extent of

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absorption. The absolute bioavailability of oral tadalafil has not been established. The mean bioavailability of the tadalafil 20 mg tablet has been estimated to be 88% relative to an oral suspension dosage form.

Distribution – The mean volume of distribution after oral dosing is approximately 63 L. 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 appears in the semen of healthy subjects.

Metabolism – Tadalafil is metabolised mainly (>80%) by the cytochrome P450 (CYP) 3A4 isoform, with minor contributions by CYPs 2C8, 2C9, 2C19 and 2D6 (<20% collectively). 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/hr 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).

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.

Table 1: Summary of Geometric Mean (CV%) Single Dose Pharmacokinetic Parameters of tadalafil (20 mg) in Healthy Volunteers

	AUC (μg*h/L)	C_{max} (μg/L)	t_{max} (h)	$t_{1/2}$ (h)
Geometric mean (CV%)	8066 (39.3)	378 (27.6)	2.0 (0.5 to 12.0)[a]	17.5 (32.3)

[a] Median and range

Pharmacokinetics in Special Populations

Elderly – Healthy elderly subjects (65 years or over) had a lower clearance of tadalafil, resulting in a half life of 22 hours and 25% higher exposure (AUC), relative to healthy subjects aged 19 to 45 years (half life of 16-17 hours). This effect does not appear to warrant a dose adjustment (see DOSAGE AND ADMINISTRATION – Elderly Patients). The half life of tadalafil in the elderly increases the period after the last dose of CIALIS during which nitrates should be avoided (see CONTRAINDICATIONS).

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Renal Impairment – In subjects with mild renal impairment (creatinine clearance 51 to 80 mL/min) or moderate renal impairment (creatinine clearance 31 to 50 mL/min), tadalafil exposure (AUC) was higher than in healthy subjects. Therefore, the recommended starting dose of tadalafil in patients with renal impairment is 10 mg (see DOSAGE and ADMINISTRATION). Tadalafil has not been studied in subjects with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see PRECAUTIONS).

Hepatic Impairment – Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No dose adjustment is required in these patients.

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.

CLINICAL TRIALS

Tadalafil when taken as needed up to once daily, is effective in improving erectile function in men with erectile dysfunction (ED). In clinical studies assessing patients' ability to engage in successful and satisfying sexual activity, tadalafil demonstrated highly statistically significant improvement compared to placebo. Additionally, partners of patients on tadalafil had statistically significant greater satisfaction with sexual activity compared to partners of patients on placebo.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients. Tadalafil 10 mg and/or 20 mg, taken as needed up to once daily, was compared to placebo in 6 primary efficacy studies (5 in a general ED population, 1 in patients with diabetes). Seven hundred and twenty four (724) patients received tadalafil 10 mg or 20 mg and 379 patients received placebo in these randomised, double blinded, parallel group studies. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted. The studies were designed in this manner in order to allow for convenience and dosing flexibility for the patient and partner.

Several assessment instruments were used to evaluate the effect of tadalafil on erectile function. Global Assessment Questions (GAQ) were asked to determine whether the treatment improved patients' erections. During clinical studies, patients and partners completed sexual encounter profile (SEP) diaries assessing erectile function and sexual satisfaction of each sexual attempt. The International Index of Erectile Function (IIEF), a recall questionnaire, was also completed by patients. The IIEF provides global measures of erectile function and sexual satisfaction, as well as severity of ED.

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In all primary efficacy studies, tadalafil demonstrated consistent and statistically significant improvement compared to placebo in all primary and secondary endpoints evaluated. In each primary efficacy study, a significant treatment effect was declared only if there was a statistically significant improvement on all three co-primary measures: 1) the IIEF Erectile Function Domain; 2) SEP Question 2 (assessing the ability to penetrate the partner's vagina); and 3) SEP Question 3 (assessing the ability to maintain the erection). The treatment effect did not diminish over time. Overall, tadalafil consistently showed efficacy in a broad and representative population that included patients with ED of various severities (mild, moderate, severe), etiologies (including patients with diabetes), ages (21 to 86 years), ethnicities and durations of ED. In the five primary efficacy studies of general populations, 81% of patients reported that tadalafil 20 mg improved their erections compared to 35% of patients on placebo. Also, patients with ED in all severity categories reported improved erections while taking tadalafil 20 mg (86%, 83% and 72% for mild, moderate and severe, respectively) compared to patients on placebo (45%, 42% and 19% for mild, moderate and severe respectively). Tadalafil showed statistically significant improvement in patients' ability to achieve an erection sufficient for sexual intercourse and maintain the erection for successful intercourse as measured by the SEP diaries. In the primary efficacy studies, 75% of intercourse attempts were successful in patients taking tadalafil 20 mg compared to 32% of patients on placebo. This finding was confirmed by partner SEP responses. Tadalafil also demonstrated statistically significant improvement in erectile function as measured by the IIEF Erectile Function Domain. Additionally, in the primary efficacy studies, approximately 60% of patients taking tadalafil 20 mg achieved normal erectile function during treatment. Patients with ED in all severity categories improved into the normal range (defined by IIEF).

Patient Confidence and Sexual Satisfaction – The IIEF also measures patients' confidence that they can attain and keep an erection sufficient for sexual intercourse. Tadalafil statistically significantly improved patient confidence. Analysis of the Intercourse Satisfaction and Overall Satisfaction domains of the IIEF showed that tadalafil treatment provided statistically significant enhancement of sexual satisfaction measured by both domains. Additionally, tadalafil improved the proportion of sexual encounters that were satisfying for both the patient and the partner.

Efficacy in ED Patients with Diabetes Mellitus – Tadalafil is effective in treating ED in patients with diabetes. Patients with diabetes (n=451) were included in all primary efficacy studies, one of which specifically assessed tadalafil only in ED patients with Type 1 or Type 2 diabetes. Tadalafil produced statistically significant improvement in erectile function and sexual satisfaction. In these studies, 68% of patients with diabetes taking tadalafil 20 mg reported improved erections.

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Period of Responsiveness – Two clinical studies were conducted in 571 patients in an at-home setting to define the period of responsiveness to tadalafil. One of the two studies specifically assessed the improvement of erectile function at 24 and 36 hours following tadalafil administration. In this study, approximately 60% of sexual attempts at both 24 and 36 hours were successful for patients on tadalafil 20 mg compared to approximately 30% of sexual attempts for patients on placebo.

Therefore, 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.

Studies of CIALIS on sperm characteristics - There were no clinically relevant effects on sperm concentration, sperm count, motility or morphology in 103 men after daily doses of tadalafil 10 mg for 6 months.

INDICATIONS

CIALIS is indicated for the treatment of erectile dysfunction in adult males. CIALIS is not indicated for use by women.

CONTRAINDICATIONS

Nitrates and tadalafil must not be used concomitantly. Co-administration of tadalafil with nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is contraindicated. Drugs which must not be used concomitantly include, but are not limited to, glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. In clinical studies, tadalafil was shown to potentiate the hypotensive effects of both acute and chronic nitrate administration. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway.

Nitrates should not be administered within 3 to 4 days in most patients and 4 to 5 days in the elderly (approximately 5 half-lives) following the last dose of CIALIS.

Tadalafil is contraindicated in men for whom sexual intercourse is inadvisable due to unstable cardiovascular disease (e.g. patients with unstable angina and severe congestive heart failure) [see PRECAUTIONS]. The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing tadalafil.

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The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- patients with a 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 should not be used in patients with a known hypersensitivity to tadalafil or to any ingredient of the tablet.

PRECAUTIONS

There are no controlled clinical data on the safety or efficacy of tadalafil in the following groups; if prescribed, this should be done with caution:

- patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min)
- patients with severe hepatic insufficiency (Child-Pugh Class C).

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

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their physician.

Tadalafil has vasodilator properties and may result in mild and transient decreases in blood pressure. Tadalafil potentiates the hypotensive effect of nitrates. Therefore, coadministration of CIALIS and nitrates is contraindicated (see CONTRAINDICATIONS). Tadalafil also potentiates the effect of some classes of antihypertensive medications, and this may be clinically important in some individuals (see PRECAUTIONS – Potential for CIALIS to Affect Other Drugs – Antihypertensive Agents).

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

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Priapism was not reported in clinical trials with tadalafil. However, priapism has been reported with another PDE5 inhibitor, sildenafil. 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 should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

In a clinical pharmacology study, administration of tadalafil 10 mg to patients with moderate renal failure (creatinine clearance = 31 to 50 mL/min) was determined to be safe but appeared to be less well tolerated in terms of back pain than in patients with mild renal failure (creatinine clearance = 51 to 80 mL/min) and in healthy subjects. Tadalafil has not been studied in patients with severe renal failure (creatinine clearance ≤ 30 mL/min). Tadalafil should be prescribed with caution for patients with creatinine clearance ≤ 50 mL/min.

Carcinogenicity and Mutagenicity

Oral administration of tadalafil at doses of 400 mg/kg/day for up to two years in mice resulted in increased development of hepatocellular adenomas in males but not in females. Tadalafil also caused hepatocellular microsomal enzyme induction in rodents and it is possible that this could lead to an increased incidence of hepatocellular neoplasms. However, hepatic microsomal enzyme induction is a common non-genotoxic biologic effect associated with hepatocellular tumour formation in rodents and is not considered relevant to human cancer risk. The no effect dose of 60 mg/kg/day was associated with systemic exposure to tadalafil approximately 5- to 7- fold that expected in men taking the maximum recommended dose of 20 mg daily, based on unbound drug concentrations.

Tadalafil was not mutagenic or genotoxic in *in vitro* bacterial and mammalian cell assays, and in *in vitro* human lymphocytes and *in vivo* rat micronucleus assays.

Impairment of Fertility

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day (systemic exposure *ca* 13 (males) or 25 (females) times that expected at the maximum recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state). However, regression of the seminiferous tubular epithelium of the testes resulting in oligospermia or aspermia in the epididymides was observed in dogs treated for 6 or 12 months with oral tadalafil doses ≥ 25 mg/kg/day. The no-observed-effect level for these

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effects in the 6-month dog study was 10 mg/kg/day. At this dose, systemic exposure to tadalafil, based on unbound drug concentrations, was similar to that expected in humans taking the maximum recommended dose of 20 mg CIALIS daily. Similar findings were not observed in rats and mice.

In a study in 103 men who received tadalafil 10 mg daily for 6 months, there was no clinically relevant effect on sperm concentration, sperm count, motility, or morphology. In men, tadalafil 10 mg given daily for 6 months had no significant effect compared to placebo on serum levels of total testosterone, free testosterone, luteinising hormone or follicle stimulating hormone.

Use in Pregnancy

Pregnancy category B1.

Tadalafil is not intended for use by women.

Studies in rats have shown that tadalafil and/or its metabolites cross the placenta and distribute to the foetus. No evidence of embryofoetal toxicity or teratogenicity was observed in pregnant rats or mice given oral doses of tadalafil up to 1000 mg/kg/day. These doses were associated with systemic exposure to tadalafil *ca* 12-14-fold that expected at the maximum recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state. Increased postnatal pup mortality was observed in rats after oral treatment with tadalafil doses ≥60 mg/kg/day during gestation and lactation. The no-effect dose of 30 mg/kg/day was associated with systemic exposure *ca* 10-fold that expected in humans at the maximum recommended dose of 20 mg tadalafil taken once daily, based on AUC for unbound drug at steady state.

There are no studies of tadalafil in pregnant women.

Use in Lactation

Tadalafil is not intended for use by women.

Tadalafil and/or its metabolites are excreted in the milk of lactating rats at concentrations up to 2.4-fold higher than the maximal maternal plasma concentration. Increased postnatal pup mortality was observed in rats after treatment with oral tadalafil doses ≥60 mg/kg/day during gestation and lactation (see Use in Pregnancy).

There are no human data on the excretion of tadalafil into breast milk or on the safety of tadalafil exposure in infants.

Interactions with Other Drugs

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

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Potential for Other Drugs to Affect CIALIS:

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole, increased tadalafil exposure (AUC) by 107%, relative to the AUC value for tadalafil (10 mg) alone. Although specific interactions have not been studied, some protease inhibitors, such as ritonavir and saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, and itraconazole should be co-administered with caution because they would be expected to increase plasma concentrations of tadalafil. A CYP3A4 inducer, rifampicin, reduced tadalafil exposure (AUC) by 88%, relative to the AUC value for tadalafil (10 mg) alone. It can be expected that concomitant administration of other CYP3A4 inducers such as phenobarbital, phenytoin and carbamazepine would also decrease plasma concentrations of tadalafil.

Studies with the CYP3A4 probe substrates midazolam with tadalafil 10 mg and lovastatin with tadalafil 20 mg showed little alteration in the kinetics suggesting that tadalafil is unlikely to have interactions with CYP3A4 substrates.

Antacids (magnesium hydroxide/aluminium hydroxide) – Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil (10 mg).

H_2 antagonists – An increase in gastric pH resulting from administration of nizatidine had no significant effect on tadalafil (10 mg) pharmacokinetics.

Potential for CIALIS to Affect Other Drugs:

Nitrates – In clinical pharmacology studies, tadalafil 10 mg was shown to potentiate the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. Nitrates should not be administered within 3 to 4 days in most patients and 4 to 5 days in the elderly (approximately 5 half-lives) following the last dose of CIALIS (see CONTRAINDICATIONS).

Antihypertensive agents – The use of tadalafil in patients taking antihypertensive medications may lead to additional blood pressure reductions, which may be clinically important in some individuals. Patients should be advised of this possibility. In a clinical pharmacology study measuring ambulatory blood pressure, when tadalafil (20 mg) was administered to 17 hypertensive patients treated with angiotensin II receptor blockers, ambulatory systolic blood pressure fell by 30 mmHg or more in 9 (53%) subjects on tadalafil treatment and in 5 (29%) subjects on placebo treatment, with a maximum fall of 57 mmHg following tadalafil compared to 37 mmHg following placebo. None of the decreases were associated with any hypotensive symptoms.

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In other clinical pharmacology studies, tadalafil 10 mg was added to angiotensin converting enzyme (ACE) inhibitors (enalapril), beta blockers (metoprolol) or thiazide diuretics (bendrofluazide). Tadalafil 10 mg and 20 mg was added to calcium channel blockers (amlodipine) or alpha-blockers (tamsulosin). In all these studies, tadalafil did not produce a significant additional reduction in mean systolic or diastolic blood pressure. However, potentially significant blood pressure reductions occurred in some individuals. Analysis of phase 3 clinical trial data showed no difference in the overall incidence of adverse events in patients taking tadalafil with or without hypertensive medications.

Human platelets contain the PDE5 enzyme system. Tadalafil, in limited studies, did not affect platelet function *in vivo*. In *in vitro* studies tadalafil was shown to potentiate the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor).

Alcohol – Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10 mg). The effects of alcohol on cognitive function and on blood pressure were not augmented by tadalafil. In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol.

Aspirin – Tadalafil (10 mg) did not potentiate the increase in bleeding time caused by aspirin.

Warfarin – In a crossover study, 12 healthy volunteers received a single dose of warfarin 25 mg after taking tadalafil 10 mg or placebo once daily for 6 days. Tadalafil reduced the exposure (AUC) to R- and S-warfarin by 11% and 13%, respectively but did not alter the effect of warfarin on prothrombin time (PT). The clinical implications of these findings are unclear. The possibility of an increase or decrease in PT and/or international normalised ratio (INR) should be considered when patients begin taking or cease taking tadalafil.

Theophylline – Tadalafil (10 mg) had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline (CYP1A2 substrate).

Effects on Ability to Drive and Operate Machinery

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 before driving or operating machinery.

Effects on Laboratory Tests

There are no data available that shows that tadalafil has an effect on laboratory tests.

CIALIS tablets contain lactose.

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ADVERSE REACTIONS

Tadalafil was administered to over 4000 subjects (ages 19 to 86 years) during clinical trials worldwide. Over 230 patients were treated for longer than one year and over 720 patients were treated for over 6 months. In controlled phase 2/3 clinical trials, the discontinuation rate due to adverse events in tadalafil-treated patients (1.7%) was not significantly different from placebo-treated patients (1.1%). In these studies, the adverse events reported with tadalafil were generally mild or moderate, transient and decreased with continued dosing. In controlled phase 2/3 clinical trials, the following adverse events were reported.

Table 2: Adverse Events Reported by ≥2% of Patients Treated with Tadalafil 10-20 mg and More Frequent on Drug than Placebo in Phase 3 Studies

Event		Tadalafil (N=724) (%)	Placebo (N=379) (%)
Nervous System	Headache	15	6
Digestive System	Dyspepsia	12	2
	Diarrhoea	2	1
Body as a Whole	Infection	8	7
Musculoskeletal	Back Pain	6	4
System	Muscle Ache	6	2
Respiratory System	Nasal Congestion	4	3
	Pharyngitis	3	2
Cardiovascular	Flushing	4	2
System			

Cardiovascular System - Common (≥ 1% and < 10%): flushing.

Digestive System – Very Common (≥ 10%): dyspepsia.

Musculoskeletal System - Common (≥ 1% and < 10%): back pain; muscle ache.

Nervous System – Very common (≥ 10%): headache. Common (≥ 1% and < 10%): dizziness.

Respiratory System – Common (≥ 1% and < 10%): nasal congestion.

Special Senses - Uncommon (≥ 0.1% and < 1%): conjunctival hyperaemia; sensations described as eye pain; swelling of eyelids.

Eye Disorders - Rare (<0.1%): changes in colour vision.

No cases of priapism were reported during controlled clinical trials.

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DOSAGE AND ADMINISTRATION

The recommended dose of CIALIS is either 10 mg or 20 mg, taken prior to anticipated sexual activity. The maximum recommended dosing frequency is once per day.
CIALIS has been proven effective up to 36 hours after dosing and, in some patients, as early as 16 minutes after dosing. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

CIALIS can be taken with or without food.

Elderly patients
Dosage adjustments are not required in elderly patients.

Patients with renal impairment
The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and without regard to food. Based on efficacy and tolerability the dose may be increased up to 20 mg.

Patients with hepatic impairment
Dosage adjustments are not required in patients with hepatic impairment.

Patients with Diabetes
Dosage adjustments are not required in patients with diabetes.

Children
Tadalafil has not been studied in subjects under 18 years of age.

OVERDOSAGE

Single doses of up to 500 mg of tadalafil have been given to healthy subjects and multiple daily doses of 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.

STORAGE

Store below 25°C. Store in the original package.

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PRESENTATION

CIALIS tablets are supplied in blister packs of 4 tablets per carton in the following strengths:
CIALIS 20 mg tablets (TA4464) and CIALIS 10 mg tablets (TA4463).

CIALIS 20 mg tablets (TA4464) and CIALIS 10 mg tablets (TA4463) are registered in blister packs of 2 and 8 tablets; these are not currently supplied in Australia.

NAME AND ADDRESS OF SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road,
West Ryde NSW 2114

TGA Approval:

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chment 1b

CIALIS®

(tadalafil)

NAME

CIALIS® (tadalafil).

Chemically, tadalafil is pyrazino[1', 2':1, 6]pyrido[3, 4-b]indole-1, 4-dione, 6-(1, 3-benzodioxol-5-yl)-2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-, (6R, 12aR)-. Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. Tadalafil is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol. The CAS number for tadalafil is 171596-29-5.

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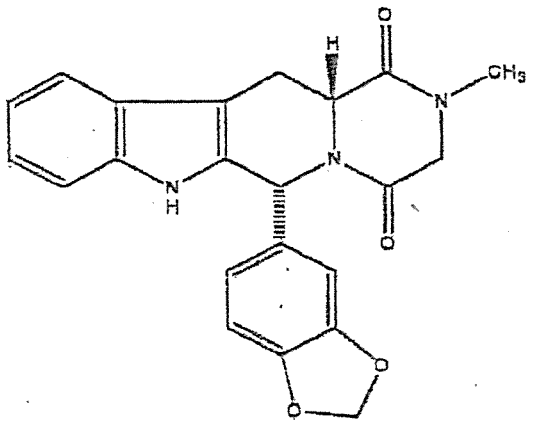

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PHARMACOLOGY

Pharmacodynamics

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oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that tadalafil inhibits PDE5 more potently than other PDEs. PDE5 is an enzyme found in the corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung and cerebellum. 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 >9,000-fold more potent for PDE5 than for PDE7 through PDE10.

Studies of CIALIS on vision – In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure or pupillometry. Across all clinical studies, reports of changes in colour vision were rare (see ADVERSE REACTIONS).

Studies of CIALIS on blood pressure and heart rate – Tadalafil administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively) and no significant change in heart rate. Larger effects were recorded among subjects receiving concomitant nitrates (see CONTRAINDICATIONS). When tadalafil and certain oral antihypertensive medications were assessed in drug interaction studies, tadalafil did not result in clinically significant augmentation of the antihypertensive effects of those medications (see PRECAUTIONS – Interactions with Other Drugs).

Pharmacokinetics

Absorption – Tadalafil is rapidly absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. There is no clinically relevant effect of food on the rate and extent of absorption of tadalafil, thus tadalafil may be taken with or without food. The time of dosing (morning versus evening) has no clinically relevant effects on the rate and extent of

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absorption. The absolute bioavailability of oral tadalafil has not been established. The mean bioavailability of the tadalafil 20 mg tablet has been estimated to be 88% relative to an oral suspension dosage form.

Distribution – The mean volume of distribution after oral dosing is approximately 63 L. 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 appears in the semen of healthy subjects.

Metabolism – Tadalafil is metabolised mainly (>80%) by the cytochrome P450 (CYP) 3A4 isoform, with minor contributions by CYPs 2C8, 2C9, 2C19 and 2D6 (<20% collectively). 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/hr 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).

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.

Table 1: Summary of Geometric Mean (CV%) Single Dose Pharmacokinetic Parameters of tadalafil (20 mg) in Healthy Volunteers

	AUC (μg*h/L)	C_{max} (μg/L)	t_{max} (h)	$t_{1/2}$ (h)
Geometric mean (CV%)	8066 (39.3)	378 (27.6)	2.0 (0.5 to 12.0)[a]	17.5 (32.3)

[a] Median and range

Pharmacokinetics in Special Populations

Elderly – Healthy elderly subjects (65 years or over) had a lower clearance of tadalafil, resulting in a half life of 22 hours and 25% higher exposure (AUC), relative to healthy subjects aged 19 to 45 years (half life of 16-17 hours). This effect does not appear to warrant a dose adjustment (see DOSAGE AND ADMINISTRATION – Elderly Patients). The half life of tadalafil in the elderly increases the period after the last dose of CIALIS during which nitrates should be avoided (see CONTRAINDICATIONS).

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Renal Impairment – In subjects with mild renal impairment (creatinine clearance 51 to 80 mL/min) or moderate renal impairment (creatinine clearance 31 to 50 mL/min), tadalafil exposure (AUC) was higher than in healthy subjects. Therefore, the recommended starting dose of tadalafil in patients with renal impairment is 10 mg (see DOSAGE and ADMINISTRATION). Tadalafil has not been studied in subjects with severe renal impairment (creatinine clearance ≤ 30 mL/min) (see PRECAUTIONS).

Hepatic Impairment – Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No dose adjustment is required in these patients.

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.

CLINICAL TRIALS

Tadalafil when taken as needed up to once daily, is effective in improving erectile function in men with erectile dysfunction (ED). In clinical studies assessing patients' ability to engage in successful and satisfying sexual activity, tadalafil demonstrated highly statistically significant improvement compared to placebo. Additionally, partners of patients on tadalafil had statistically significant greater satisfaction with sexual activity compared to partners of patients on placebo.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients. Tadalafil 10 mg and/or 20 mg, taken as needed up to once daily, was compared to placebo in 6 primary efficacy studies (5 in a general ED population, 1 in patients with diabetes). Seven hundred and twenty four (724) patients received tadalafil 10 mg or 20 mg and 379 patients received placebo in these randomised, double blinded, parallel group studies. Patients were free to choose the time interval between dose administration and the time of sexual attempts. Food and alcohol intake were not restricted. The studies were designed in this manner in order to allow for convenience and dosing flexibility for the patient and partner.

Several assessment instruments were used to evaluate the effect of tadalafil on erectile function. Global Assessment Questions (GAQ) were asked to determine whether the treatment improved patients' erections. During clinical studies, patients and partners completed sexual encounter profile (SEP) diaries assessing erectile function and sexual satisfaction of each sexual attempt. The International Index of Erectile Function (IIEF), a

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recall questionnaire, was also completed by patients. The IIEF provides global measures of erectile function and sexual satisfaction, as well as severity of ED.

In all primary efficacy studies, tadalafil demonstrated consistent and statistically significant improvement compared to placebo in all primary and secondary endpoints evaluated. In each primary efficacy study, a significant treatment effect was declared only if there was a statistically significant improvement on all three co-primary measures: 1) the IIEF Erectile Function Domain; 2) SEP Question 2 (assessing the ability to penetrate the partner's vagina); and 3) SEP Question 3 (assessing the ability to maintain the erection). The treatment effect did not diminish over time. Overall, tadalafil consistently showed efficacy in a broad and representative population that included patients with ED of various severities (mild, moderate, severe), etiologies (including patients with diabetes), ages (21 to 86 years), ethnicities and durations of ED. In the five primary efficacy studies of general populations, 81% of patients reported that tadalafil 20 mg improved their erections compared to 35% of patients on placebo. Also, patients with ED in all severity categories reported improved erections while taking tadalafil 20 mg (86%, 83% and 72% for mild, moderate and severe, respectively) compared to patients on placebo (45%, 42% and 19% for mild, moderate and severe respectively). Tadalafil showed statistically significant improvement in patients' ability to achieve an erection sufficient for sexual intercourse and maintain the erection for successful intercourse as measured by the SEP diaries. In the primary efficacy studies, 75% of intercourse attempts were successful in patients taking tadalafil 20 mg compared to 32% of patients on placebo. This finding was confirmed by partner SEP responses. Tadalafil also demonstrated statistically significant improvement in erectile function as measured by the IIEF Erectile Function Domain. Additionally, in the primary efficacy studies, approximately 60% of patients taking tadalafil 20 mg achieved normal erectile function during treatment. Patients with ED in all severity categories improved into the normal range (defined by IIEF).

Patient Confidence and Sexual Satisfaction – The IIEF also measures patients' confidence that they can attain and keep an erection sufficient for sexual intercourse. Tadalafil statistically significantly improved patient confidence. Analysis of the Intercourse Satisfaction and Overall Satisfaction domains of the IIEF showed that tadalafil treatment provided statistically significant enhancement of sexual satisfaction measured by both domains. Additionally, tadalafil improved the proportion of sexual encounters that were satisfying for both the patient and the partner.

Efficacy in ED Patients with Diabetes Mellitus – Tadalafil is effective in treating ED in patients with diabetes. Patients with diabetes (n=451) were included in all primary efficacy studies, one of which specifically assessed tadalafil only in ED patients with Type 1 or Type 2 diabetes. Tadalafil produced statistically significant improvement in erectile function and

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sexual satisfaction. In these studies, 68% of patients with diabetes taking tadalafil 20 mg reported improved erections.

Period of Responsiveness – Two clinical studies were conducted in 571 patients in an at-home setting to define the period of responsiveness to tadalafil. One of the two studies specifically assessed the improvement of erectile function at 24 and 36 hours following tadalafil administration. In this study, approximately 60% of sexual attempts at both 24 and 36 hours were successful for patients on tadalafil 20 mg compared to approximately 30% of sexual attempts for patients on placebo.

Therefore, 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.

Studies of CIALIS on sperm characteristics - There were no clinically relevant effects on sperm concentration, sperm count, motility or morphology in 103 men after daily doses of tadalafil 10 mg for 6 months.

INDICATIONS

CIALIS is indicated for the treatment of erectile dysfunction in adult males. CIALIS is not indicated for use by women.

CONTRAINDICATIONS

Nitrates and tadalafil must not be used concomitantly. Co-administration of tadalafil with nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is contraindicated. Drugs which must not be used concomitantly include, but are not limited to, glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. In clinical studies, tadalafil was shown to potentiate the hypotensive effects of both acute and chronic nitrate administration. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway.

Nitrates should not be administered within 3 to 4 days in most patients and 4 to 5 days in the elderly (approximately 5 half-lives) following the last dose of CIALIS.

Tadalafil is contraindicated in men for whom sexual intercourse is inadvisable due to unstable cardiovascular disease (e.g. patients with unstable angina and severe congestive heart failure) [see PRECAUTIONS]. The possibility of undiagnosed cardiovascular

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disorders in men with erectile dysfunction should be considered before prescribing tadalafil.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- patients with a 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 should not be used in patients with a known hypersensitivity to tadalafil or to any ingredient of the tablet.

PRECAUTIONS

There are no controlled clinical data on the safety or efficacy of tadalafil in the following groups; if prescribed, this should be done with caution:

- patients with severe renal insufficiency (creatinine clearance ≤ 30 mL/min)
- patients with severe hepatic insufficiency (Child-Pugh Class C).

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

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their physician.

Tadalafil has vasodilator properties and may result in mild and transient decreases in blood pressure. Tadalafil potentiates the hypotensive effect of nitrates. Therefore, coadministration of CIALIS and nitrates is contraindicated (see CONTRAINDICATIONS). Tadalafil also potentiates the effect of some classes of antihypertensive medications, and this may be clinically important in some individuals (see PRECAUTIONS – Potential for CIALIS to Affect Other Drugs – Antihypertensive Agents).

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

Priapism was not reported in clinical trials with tadalafil. However, priapism has been reported with another PDE5 inhibitor, sildenafil. 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 should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anaemia, multiple myeloma, or leukaemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

In a clinical pharmacology study, administration of tadalafil 10 mg to patients with moderate renal failure (creatinine clearance = 31 to 50 mL/min) was determined to be safe but appeared to be less well tolerated in terms of back pain than in patients with mild renal failure (creatinine clearance = 51 to 80 mL/min) and in healthy subjects. Tadalafil has not been studied in patients with severe renal failure (creatinine clearance ≤ 30 mL/min). Tadalafil should be prescribed with caution for patients with creatinine clearance ≤ 50 mL/min.

Carcinogenicity and Mutagenicity

Oral administration of tadalafil at doses of 400 mg/kg/day for up to two years in mice resulted in increased development of hepatocellular adenomas in males but not in females. Tadalafil also caused hepatocellular microsomal enzyme induction in rodents and it is possible that this could lead to an increased incidence of hepatocellular neoplasms. However, hepatic microsomal enzyme induction is a common non-genotoxic biologic effect associated with hepatocellular tumour formation in rodents and is not considered relevant to human cancer risk. The no effect dose of 60 mg/kg/day was associated with systemic exposure to tadalafil approximately 5- to 7- fold that expected in men taking the maximum recommended dose of 20 mg daily, based on unbound drug concentrations.

Tadalafil was not mutagenic or genotoxic in *in vitro* bacterial and mammalian cell assays, and in *in vitro* human lymphocytes and *in vivo* rat micronucleus assays.

Impairment of Fertility

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day (systemic exposure *ca* 13 (males) or 25 (females) times that expected at the maximum

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recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state). However, regression of the seminiferous tubular epithelium of the testes resulting in oligospermia or aspermia in the epididymides was observed in dogs treated for 6 or 12 months with oral tadalafil doses ≥ 25 mg/kg/day. The no-observed-effect level for these effects in the 6-month dog study was 10 mg/kg/day. At this dose, systemic exposure to tadalafil, based on unbound drug concentrations, was similar to that expected in humans taking the maximum recommended dose of 20 mg CIALIS daily. Similar findings were not observed in rats and mice.

In a study in 103 men who received tadalafil 10 mg daily for 6 months, there was no clinically relevant effect on sperm concentration, sperm count, motility, or morphology. In men, tadalafil 10 mg given daily for 6 months had no significant effect compared to placebo on serum levels of total testosterone, free testosterone, luteinising hormone or follicle stimulating hormone.

Use in Pregnancy

Pregnancy category B1.

Tadalafil is not intended for use by women.

Studies in rats have shown that tadalafil and/or its metabolites cross the placenta and distribute to the foetus. No evidence of embryofoetal toxicity or teratogenicity was observed in pregnant rats or mice given oral doses of tadalafil up to 1000 mg/kg/day. These doses were associated with systemic exposure to tadalafil *ca* 12-14-fold that expected at the maximum recommended dose of 20 mg taken once daily, based on AUC for unbound drug at steady state. Increased postnatal pup mortality was observed in rats after oral treatment with tadalafil doses ≥60 mg/kg/day during gestation and lactation. The no-effect dose of 30 mg/kg/day was associated with systemic exposure *ca* 10-fold that expected in humans at the maximum recommended dose of 20 mg tadalafil taken once daily, based on AUC for unbound drug at steady state.

There are no studies of tadalafil in pregnant women.

Use in Lactation

Tadalafil is not intended for use by women.

Tadalafil and/or its metabolites are excreted in the milk of lactating rats at concentrations up to 2.4-fold higher than the maximal maternal plasma concentration. Increased postnatal pup mortality was observed in rats after treatment with oral tadalafil doses ≥60 mg/kg/day during gestation and lactation (see Use in Pregnancy). There are no human data on the excretion of tadalafil into breast milk or on the safety of tadalafil exposure in infants.

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Interactions with Other Drugs

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

Potential for Other Drugs to Affect CIALIS:

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole, increased tadalafil exposure (AUC) by 107%, relative to the AUC value for tadalafil (10 mg) alone. Although specific interactions have not been studied, some protease inhibitors, such as ritonavir and saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, and itraconazole should be co-administered with caution because they would be expected to increase plasma concentrations of tadalafil. A CYP3A4 inducer, rifampicin, reduced tadalafil exposure (AUC) by 88%, relative to the AUC value for tadalafil (10 mg) alone. It can be expected that concomitant administration of other CYP3A4 inducers such as phenobarbital, phenytoin and carbamazepine would also decrease plasma concentrations of tadalafil.

Studies with the CYP3A4 probe substrates midazolam with tadalafil 10 mg and lovastatin with tadalafil 20 mg showed little alteration in the kinetics suggesting that tadalafil is unlikely to have interactions with CYP3A4 substrates.

Antacids (magnesium hydroxide/aluminium hydroxide) – Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil (10 mg).

H_2 antagonists – An increase in gastric pH resulting from administration of nizatidine had no significant effect on tadalafil (10 mg) pharmacokinetics.

Potential for CIALIS to Affect Other Drugs:

Nitrates – In clinical pharmacology studies, tadalafil 10 mg was shown to potentiate the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. Nitrates should not be administered within 3 to 4 days in most patients and 4 to 5 days in the elderly (approximately 5 half-lives) following the last dose of CIALIS (see CONTRAINDICATIONS).

Antihypertensive agents – The use of tadalafil in patients taking antihypertensive medications may lead to additional blood pressure reductions, which may be clinically important in some individuals. Patients should be advised of this possibility. In a clinical pharmacology study measuring ambulatory blood pressure, when tadalafil (20 mg) was administered to

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17 hypertensive patients treated with angiotensin II receptor blockers, ambulatory systolic blood pressure fell by 30 mmHg or more in 9 (53%) subjects on tadalafil treatment and in 5 (29%) subjects on placebo treatment, with a maximum fall of 57 mmHg following tadalafil compared to 37 mmHg following placebo. None of the decreases were associated with any hypotensive symptoms.

In other clinical pharmacology studies, tadalafil 10 mg was added to angiotensin converting enzyme (ACE) inhibitors (enalapril), beta blockers (metoprolol) or thiazide diuretics (bendrofluazide). Tadalafil 10 mg and 20 mg was added to calcium channel blockers (amlodipine) or alpha-blockers (tamsulosin). In all these studies, tadalafil did not produce a significant additional reduction in mean systolic or diastolic blood pressure. However, potentially significant blood pressure reductions occurred in some individuals. Analysis of phase 3 clinical trial data showed no difference in the overall incidence of adverse events in patients taking tadalafil with or without hypertensive medications.

Human platelets contain the PDE5 enzyme system. Tadalafil, in limited studies, did not affect platelet function *in vivo*. In *in vitro* studies tadalafil was shown to potentiate the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor).

Alcohol – Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10 mg). The effects of alcohol on cognitive function and on blood pressure were not augmented by tadalafil. In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol.

Aspirin – Tadalafil (10 mg) did not potentiate the increase in bleeding time caused by aspirin.

Warfarin –In a crossover study, 12 healthy volunteers received a single dose of warfarin 25 mg after taking tadalafil 10 mg or placebo once daily for 6 days. Tadalafil reduced the exposure (AUC) to R- and S-warfarin by 11% and 13%, respectively but did not alter the effect of warfarin on prothrombin time (PT). The clinical implications of these findings are unclear. The possibility of an increase or decrease in PT and/or international normalised ratio (INR) should be considered when patients begin taking or cease taking tadalafil.

Theophylline – Tadalafil (10 mg) had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline (CYP1A2 substrate).

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Effects on Ability to Drive and Operate Machinery

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 before driving or operating machinery.

Effects on Laboratory Tests

There are no data available that shows that tadalafil has an effect on laboratory tests.

CIALIS tablets contain lactose.

ADVERSE REACTIONS

Tadalafil was administered to over 4000 subjects (ages 19 to 86 years) during clinical trials worldwide. Over 230 patients were treated for longer than one year and over 720 patients were treated for over 6 months. In controlled phase 2/3 clinical trials, the discontinuation rate due to adverse events in tadalafil-treated patients (1.7%) was not significantly different from placebo-treated patients (1.1%). In these studies, the adverse events reported with tadalafil were generally mild or moderate, transient and decreased with continued dosing. In controlled phase 2/3 clinical trials, the following adverse events were reported.

Table 2: Adverse Events Reported by ≥2% of Patients Treated with Tadalafil 10-20 mg and More Frequent on Drug than Placebo in Phase 3 Studies

Event		Tadalafil (N=724) (%)	Placebo (N=379) (%)
Nervous System	Headache	15	6
Digestive System	Dyspepsia	12	2
	Diarrhoea	2	1
Body as a Whole	Infection	8	7
Musculoskeletal	Back Pain	6	4
System	Muscle Ache	6	2
Respiratory System	Nasal Congestion	4	3
	Pharyngitis	3	2
Cardiovascular	Flushing	4	2
System			

Cardiovascular System - Common (≥ 1% and < 10%): flushing.

Digestive System – Very Common (≥ 10%): dyspepsia.

Musculoskeletal System - Common (≥ 1% and < 10%): back pain; muscle ache.

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Nervous System – Very common (≥ 10%): headache. Common (≥ 1% and < 10%): dizziness.

Respiratory System – Common (≥ 1% and < 10%): nasal congestion.

Special Senses - Uncommon (≥ 0.1% and < 1%): conjunctival hyperaemia; sensations described as eye pain; swelling of eyelids.

Eye Disorders - Rare (<0.1%): changes in colour vision.

No cases of priapism were reported during controlled clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of CIALIS is either 10 mg or 20 mg, taken prior to anticipated sexual activity. The maximum recommended dosing frequency is once per day.
CIALIS has been proven effective up to 36 hours after dosing and, in some patients, as early as 16 minutes after dosing. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

CIALIS can be taken with or without food.

Elderly patients
Dosage adjustments are not required in elderly patients.

Patients with renal impairment
The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and without regard to food. Based on efficacy and tolerability the dose may be increased up to 20 mg.

Patients with hepatic impairment
Dosage adjustments are not required in patients with hepatic impairment.

Patients with Diabetes
Dosage adjustments are not required in patients with diabetes.

Children
Tadalafil has not been studied in subjects under 18 years of age.

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OVERDOSAGE

Single doses of up to 500 mg of tadalafil have been given to healthy subjects and multiple daily doses of 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.

STORAGE

Store below 25°C. Store in the original package.

PRESENTATION

CIALIS tablets are supplied in blister packs of 4 tablets per carton in the following strengths:
CIALIS 20 mg tablets (TA4464) and CIALIS 10 mg tablets (TA4463).

NAME AND ADDRESS OF SPONSOR

Eli Lilly Australia Pty. Limited
112 Wharf Road,
West Ryde NSW 2114

TGA Approval:

15 OCT 2002
Dr O. Tinnion