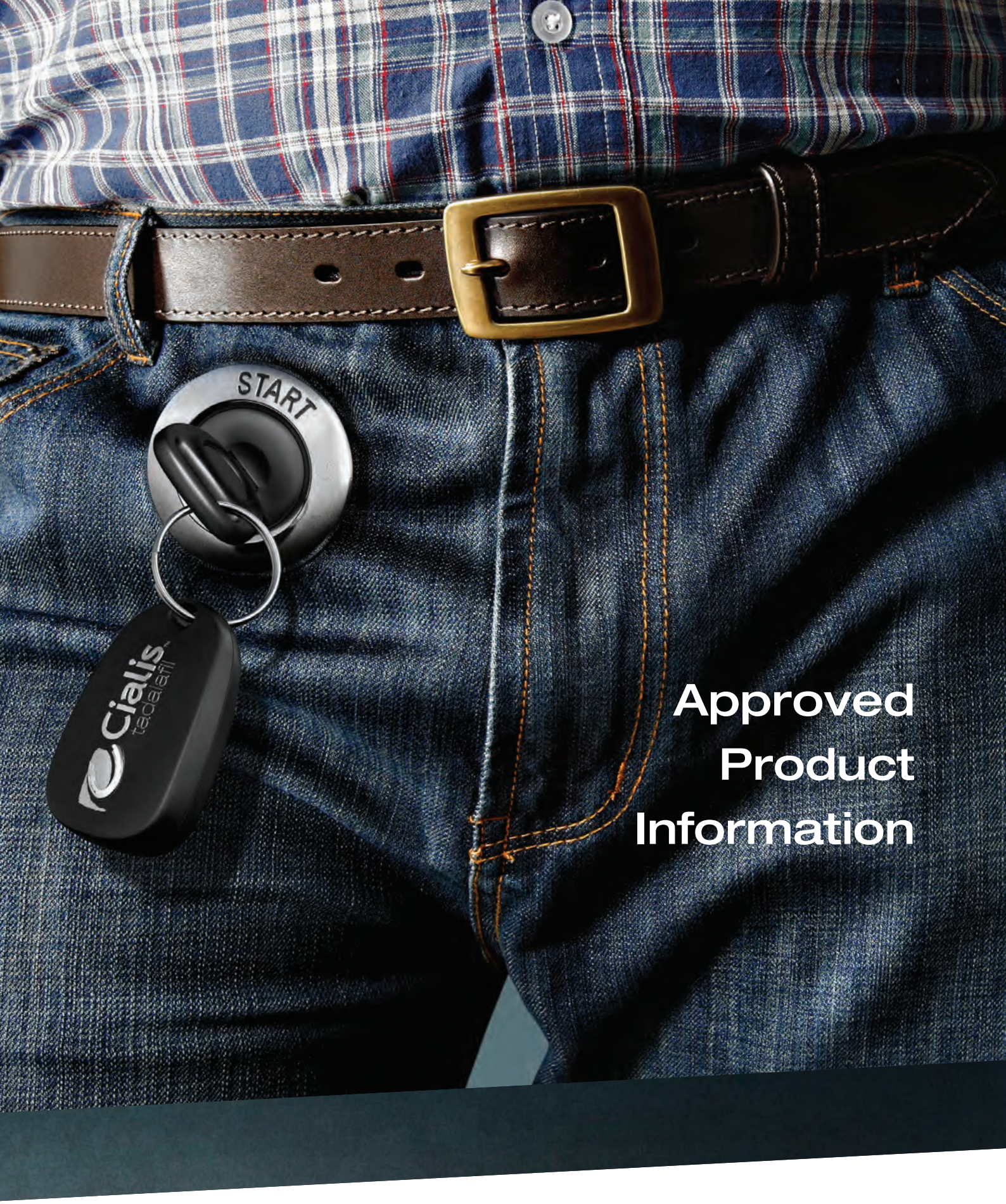



# Approved Product Information

Cialis™ tadalafil

# Cialis Approved Product Information

# Cialis®

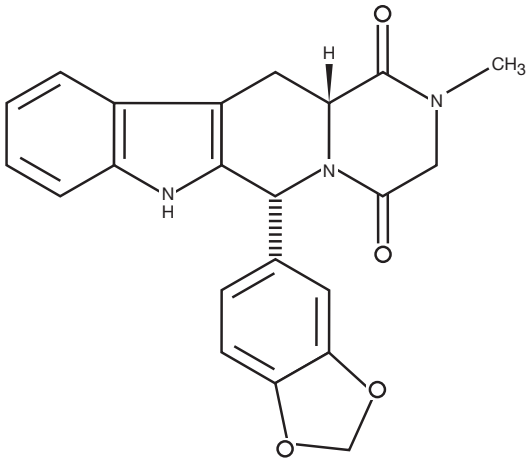
***tadalafil***

## 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. CIALIS 5 mg tablets are light yellow, film coated, almond shaped tablets for oral administration, marked "C 5" on one side. CIALIS 2.5 mg tablets are light orange-yellow, film coated, almond shaped tablets for oral administration, marked "C 2 ½" on one side. The active ingredient in CIALIS tablets is tadalafil. CIALIS tablets also contain the following excipients: croscarmellose sodium, hydroxypropylcellulose, hypromellose, lactose, magnesium stearate, cellulose - microcrystalline, sodium lauryl sulfate, talc - purified, titanium dioxide and glycerol triacetate. CIALIS 10 mg and 20 mg tablets also contain iron oxide yellow CI77492. CIALIS 5 mg tablets also contain Opadry II complete film coating system Y-30-12863-A Yellow. Cialis 2.5mg tablets also contain Opadry II complete film coating system 32K12891 Yellow.

## 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 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, PDE4, and PDE7 enzymes which are found in the heart, brain, blood vessels, liver, leukocytes, skeletal muscle 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 PDE8, 9 and 10 and 14-fold more potent for PDE5 than for PDE11. The tissue distribution and physiological effects of the inhibition of PDE8 through PDE11 have not been elucidated.

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 EFFECTS).

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).

Studies on Spermatogenesis – Three studies were conducted in men to assess the potential effect on spermatogenesis of tadalafil 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. There were no adverse effects on sperm morphology or sperm motility in any of the three studies. In the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months, results showed a decrease in mean sperm concentrations relative to placebo. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In all 3 studies there were no statistically significant differences between the placebo and tadalafil groups for mean total sperm counts. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinising hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

**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 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).

Renal Impairment – In subjects with renal insufficiency, including those on haemodialysis, tadalafil exposure (AUC) was higher than in healthy subjects. Therefore, the recommended starting dose of tadalafil in patients with mild or moderate renal impairment is 10 mg. For patients with severe renal impairment 10 mg is the maximum recommended dose (see DOSAGE and ADMINISTRATION).

A single dose study in 8 men suffering from End Stage Renal Disease who were stable on haemodialysis showed 3-4 fold increase in AUC and 2-2.5 fold increase in $C_{max}$ in tadalafil levels. The half-life of the drug is also prolonged.

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 controlled data are available in patients with severe hepatic impairment (Child-Pugh Class C). Once-a-day administration has not been evaluated in patients with hepatic insufficiency. If tadalafil is prescribed, 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.

**CLINICAL TRIALS**

**On-Demand Dosing for the Treatment of Erectile Dysfunction**

Tadalafil when taken on demand 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 on demand 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. 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.

Period of Responsiveness – The diary data from 11 previous efficacy studies in the general ED population was combined to define the period of responsiveness. There were 321, 1143, and 638 patients in the 10 mg, 20 mg tadalafil and placebo group respectively. The response appeared as early as <1 hour. At 24 hours, 71% & 72% of attempts at sexual intercourse were successful with 10 mg (n=76) and 20 mg (n=366) tadalafil respectively. The success rate at 36 hours was 72% and 75% with 10 mg (n=34) and 20 mg (n=129) tadalafil respectively. The success rate with placebo was 44% (n=135) and 47% (n=46) at 24 and 36 hours post-dose respectively. 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.

**Once-a-Day Dosing for the Treatment of Erectile Dysfunction**

Tadalafil at doses of 2.5, 5, and 10 mg taken once a day has been evaluated in 3 clinical studies involving 853 patients of various ages (range 21-82 years) and ethnicities, with erectile dysfunction of various severities (mild, moderate, severe) and etiologies. In the two primary efficacy studies of general populations, 76 and 85% of patients reported that tadalafil 5 mg taken once a day improved their erections as compared to 29 and 30% with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections while taking tadalafil once a day. In the primary efficacy studies, 62 and 69% of intercourse attempts in the general population studies were successful in tadalafil 5 mg-treated patients as compared to 34 and 39% with placebo. Tadalafil 5 mg significantly improves erectile function over the 24-hour period between the doses.

## 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.

Administration of tadalafil to patients who are using any form of organic nitrate is contraindicated. In a patient prescribed CIALIS where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours in most patients and 4-5 days in the elderly (approximately 4-5 half lives) should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring (see PRECAUTIONS- Interactions with Other Drugs).

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.

Tadalafil is contraindicated in patients who have loss of vision in one eye because of nonarteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see PRECAUTIONS).

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

Caution should be exercised when prescribing CIALIS to patients with severe hepatic insufficiency (Child-Pugh Class C) or to those taking CYP3A4 inhibitors or HIV protease inhibitors.

Once-a-day administration has not been evaluated extensively in patients with hepatic insufficiency. If tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

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.

As with other PDE5 inhibitors, tadalafil has systemic vasodilatory properties that may result in mild and transient decreases in blood pressure. Prior to prescribing CIALIS, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by vasodilatory effects. 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. When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy. (see PRECAUTIONS – Potential for CIALIS to Affect Other Drugs – Antihypertensive Agents).

Specific studies examining potential withdrawal effects from daily use have not been conducted. Rebound effects on blood pressure have not been observed after follow-up assessments at 2 weeks and 4 weeks following cessation of up to 1 year of chronic daily treatment of CIALIS. Blood pressure was not specifically monitored leading up to or between the 2 and 4 weeks posttreatment assessments. Based upon the limited clinical data examining withdrawal effects, it is recommended that physicians continue monitoring the cardiovascular status, including blood pressure changes, of their patients after discontinuation of CIALIS.

Physicians should advise patients to stop taking PDE5 inhibitors, including CIALIS, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including CIALIS. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see ADVERSE EFFECTS).

Caution should be exercised when prescribing CIALIS to patients who are taking alpha[1] blockers, such as doxazosin, as simultaneous administration may lead to symptomatic hypotension in some patients (See PRECAUTIONS – Potential for CIALIS to Affect Other Drugs). The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Priapism has been reported with PDE5 inhibitors, including tadalafil. 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. In a single dose, pharmacodynamic study of 8 patients with End Stage Renal Disease who were stable on haemodialysis, the reported adverse effects included headache, dizziness, and somnolence.

Tadalafil should be prescribed with caution for patients with creatinine clearance < 50 mL/min.

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 is not recommended in patients with severe renal impairment.

Physicians should advise patients to stop use of all PDE5 inhibitors, including CIALIS, and seek medical attention in the event of a sudden loss of vision in one or both eyes (see CONTRAINDICATIONS). Such an event may be a sign of non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors (see ADVERSE EFFECTS - Adverse events identified from spontaneous post marketing surveillance).

Effects on 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 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 (see Pharmacodynamics).

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.

Carcinogenicity

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.

Genotoxicity

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.

Interactions with Other Medicines

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 CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

**Potential for Other Drugs to Affect CIALIS:**

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (400 mg daily), increased tadalafil single-dose exposure (AUC) by 312% and $C_{max}$ by 22%, and ketaconazole (200 mg daily), increased tadalafil single-dose exposure (AUC) by 107%, and $C_{max}$ by 15% relative to the AUC and $C_{max}$ values for tadalafil (10 mg) alone. Ritonavir (200 mg twice daily), an inhibitor of CYP3A4, 2C9, 2C19, and 2D6, increased tadalafil single-dose exposure (AUC) by 124% with no change in $C_{max}$. Although specific interactions have not been studied, other HIV protease inhibitors such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice should be co-administered with caution because they would be expected to increase plasma concentrations of tadalafil. A selective CYP3A4 inducer, rifampicin (600 mg daily), reduced tadalafil single-dose exposure (AUC) by 88%, and $C_{max}$ by 46% relative to the AUC and $C_{max}$ values for tadalafil (10 mg) alone. This reduced exposure can be anticipated to decrease the efficacy of once-a-day-dosed tadalafil; the magnitude of decreased efficacy is unknown. It can be expected that concomitant administration of other CYP3A4 inducers such as phenobarbitone, 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).

H2 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. A placebo-controlled study was conducted to assess the degree of interaction between nitroglycerine and tadalafil. One hundred and fifty subjects received daily doses of tadalafil 20 mg for 7 days. On the 7th day, 0.4 mg sublingual nitroglycerine was given at various times following the daily dose of tadalafil. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed (see CONTRAINDICATIONS).

Recreational Drugs called “poppers” or “amyl” – Due to the known interaction between tadalafil and nitrates or other nitric oxide donors on nitrogen monoxide/cGMP metabolism, patients must be expressly informed that they should never use recreational drugs called “poppers” or “amyl”, typically taken through inhalation. These drugs represent various alkyl nitrites including amyl nitrite, butyl nitrite and isobutyl nitrite.

Antihypertensive agents – Tadalafil has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive agents. 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. Additionally, in patients taking multiple antihypertensive agents whose hypertension was not well controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. Appropriate clinical advice should be given to patients when they are treated with antihypertensive medications and CIALIS.

When initiating daily treatment with tadalafil, appropriate clinical considerations should be given to a possible dose adjustment of the antihypertensive therapy.

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.

In two clinical pharmacology studies, no significant decreases in blood pressure were observed when tadalafil was co-administered to healthy subjects taking the selective alpha[1A]adrenergic blocker, tamsulosin.

In three clinical pharmacology studies when tadalafil was co-administered to healthy subjects taking doxazosin (4-8 mg daily), an alpha[1]-adrenergic blocker, there was an augmentation of the blood-pressure-lowering effect of doxazosin. The number of patients with potentially clinically significant standing-blood-pressure decreases was greater for the combination. In these clinical pharmacology studies there were symptoms associated with the decrease in blood pressure including syncope.

Caution is advised when PDE5 inhibitors are coadministered with nonselective alpha ($\alpha$1)blockers. PDE5 inhibitors, including CIALIS, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following;

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest recommended dose.
- In those patients already taking an optimized dose of PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

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 – Tadalafil did not affect alcohol concentrations, and alcohol did not affect tadalafil concentrations. At high doses of alcohol (0.7 g/kg), the addition of tadalafil 20 mg did not induce statistically significant mean blood pressure decreases. 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.

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.

Ethinylestradiol – 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.

Theophylline – Tadalafil (10 mg) had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline (CYP1A2 substrate). The only pharmadynamic effect was a small (3.5 bpm) increase in heart rate.

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 EFFECTS

**Adverse events identified from clinical trials**

On-Demand Dosing

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.

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

**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 System** | Back Pain | 7 | 4 |
| | Muscle Ache | 6 | 2 |
| **Respiratory System** | Nasal Congestion | 4 | 3 |
| | Pharyngitis | 3 | 2 |
| **Cardiovascular System** | Flushing | 4 | 2 |
| **Nervous System** | – Common: dizziness | | |
| **Special Senses** | – Uncommon: conjunctival hyperaemia; sensations described as eye pain; swelling of eyelids. | | |
| **Eye Disorders** | – Rare: changes in colour vision. | | |
| **Ear and labyrinth disorders** | – Uncommon: sudden decrease or loss of hearing[(a)] | | |

[(a)] Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the ear and labyrinth adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Once-a-day Dosing

**Table 3: Adverse events reported by patients treated with Tadalafil 2.5-5 mg and more frequent on drug than placebo in phase 3 studies**

| Event | | Tadalafil (N=500) (%) | Placebo (N=248) (%) |
|---|---|---|---|
| **Respiratory System** | Nasal Congestion | 1.8 | 0 |
| **Digestive System** | Dyspepsia | 4 | 1.6 |
| **Musculoskeletal System** | Back Pain | 3 | 1.2 |
| | Myalgia | 2.2 | 1.2 |
| **Cardiovascular System** | Flushing | 2 | 0.8 |

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.

**Adverse events identified from spontaneous post marketing surveillance**

On-Demand Dosing

**Body as a whole**

Uncommon; hypersensitivity reactions including rash and urticaria

Rare; facial oedema

Frequency not known; Stevens-Johnson syndrome and exfoliative dermatitis

**Cardiac Disorders**[b]

Uncommon; palpitations, tachycardia, chest pain

Rare; myocardial infarction

Frequency not known; unstable angina pectoris, ventricular arrhythmia, sudden cardiac death

[b]Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether these events are related directly to these factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

**Vascular Disorders**

Uncommon; hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension

**Gastrointestinal**

Common; abdominal pain

Uncommon; gastroesophageal reflux

**Skin and subcutaneous tissue**

Uncommon; hyperhidrosis (sweating)

**Special Senses**

Uncommon; blurred vision

Rare; visual field defect

Frequency not known: non-arteritic anterior ischemic optic neuropathy (NAION), retinal vascular occlusion.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including CIALIS. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

**Urogenital System**

Rare; prolonged erections

Frequency not known; priapism, spontaneous penile erection

**Nervous System**

Very common; headache

Common; dizziness

Rare; stroke[b], migraine, syncope, transient ischemic attacks[b]

Frequency not known; seizures

[b]Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to determine whether these events are related directly to these factors, to tadalafil, to sexual activity, or to a combination of these or other factors.

**Respiratory System**

Uncommon; epistaxis

**Ear and labyrinth disorders**

Very rare; sudden decrease or loss of hearing[a]

[a]Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trial cases with the use of all PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the ear and labyrinth adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

## DOSAGE AND ADMINISTRATION

**On-Demand Dosing:**

The recommended dose of CIALIS is either 10 mg or 20 mg, taken prior to anticipated sexual activity. The maximum recommended dose is 20 mg. The maximum recommended dosing frequency is once per day. CIALIS 10 and 20 mg is intended for use prior to anticipated sexual activity and is not for continuous daily use.

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.

**Patients with renal impairment**

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity and without regard to food for patients with mild or moderate renal impairment. Based on efficacy and tolerability the dose may be increased up to 20 mg. For patients with severe renal impairment 10 mg is the maximum recommended dose.

**Patients with hepatic impairment**

The recommended dose of CIALIS is 10 mg taken prior to anticipated sexual activity with or without food for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B). There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment. There is limited clinical data on the safety of CIALIS in patients with severe hepatic impairment (Child-Pugh Class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. (Refer to Pharmacokinetics in Special Populations – Hepatic Impairment)

**Once-a-Day Dosing:**

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

In these patients the recommended dose is 5mg taken once a day at approximately the same time of day. The dose must not exceed 5mg daily. The dose may be decreased to 2.5mg once a day based on individual tolerability.

There is insufficient evidence on the maximum duration of treatment. The appropriateness of continued use of the once-a-day regimen should be reassessed periodically.

**Patients with renal impairment**

Dosage adjustments are not required in patients with mild or moderate renal impairment. Once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

**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 (Refer to Pharmacokinetics in Special Populations – Hepatic Impairment).

**Patients with Diabetes**

Dosage adjustments are not required in patients with diabetes.

**Elderly Patients**

Dosage adjustments are not required in elderly patients.

**Children**

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

CIALIS can be taken with or without food.

## 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. Haemodialysis contributes negligibly to tadalafil elimination. In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766) for advice.

## PRESENTATION AND STORAGE CONDITIONS

CIALIS 20 mg tablets are presented in blister packs of 2*, 4 and 8 tablets per carton.

CIALIS 10 mg tablets are presented in blister packs of 2*, 4 and 8* tablets per carton.

CIALIS 5 mg tablets are presented in blister packs of 28 tablets per carton

*CIALIS 2.5mg are presented in blister packs of 28 tablets per carton.

*not currently available

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

## NAME AND ADDRESS OF SPONSOR

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

## POISON SCHEDULE OF THE MEDICINE

S4

## DATE OF APPROVAL

TGA Approval: 18 January 2008

Date of Most Recent Amendment: 24 September 2009

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