

**SUMMARY OF
PRODUCT
CHARACTERISTICS**



1. TRADE NAME OF THE MEDICINAL PRODUCT

Cialis* 10mg film-coated tablets.

Cialis 20mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10mg tablet contains 10mg tadalafil.

Each 20mg tablet contains 20mg tadalafil.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction.

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

Cialis is not indicated for use by women.

4.2 Posology and method of administration

For oral use.

USE IN ADULT MEN

The recommended dose is 10mg taken prior to anticipated sexual activity and without regard to food. In those patients in whom tadalafil 10mg does not produce an adequate effect, 20mg might be tried. It can be taken from 30 minutes to 12 hours prior to sexual activity. Efficacy of tadalafil may persist up to 24 hours post-dose.

The maximum recommended dosing frequency is once per day.

Daily use of the medication is strongly discouraged because the long-term safety after prolonged daily dosing has not been established. See section 4.4, 'Special warnings and special precautions for use', last paragraph.

USE IN ELDERLY MEN

Dosage adjustments are not required in elderly patients.

USE IN MEN WITH IMPAIRED RENAL FUNCTION

The recommended dose of Cialis is 10mg taken prior to anticipated

sexual activity and without regard to food. There are no available data about the administration of doses higher than 10mg of tadalafil to patients with renal impairment. (See sections 4.4, 'Special warnings and special precautions for use', and 5.2, 'Pharmacokinetic properties'.)

USE IN MEN WITH IMPAIRED HEPATIC FUNCTION

The recommended dose of Cialis is 10mg taken prior to anticipated sexual activity and without regard to food. There are no available data about the administration of doses higher than 10mg of tadalafil to patients with hepatic impairment. (See sections 4.4, 'Special warnings and special precautions for use', and 5.2, 'Pharmacokinetic properties'.)

USE IN MEN WITH DIABETES

Dosage adjustments are not required in diabetic patients.

USE IN CHILDREN AND ADOLESCENTS

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

4.3 Contra-indications

In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. Therefore, administration of Cialis to patients who are using any form of organic nitrate is contra-indicated.

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

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

- Patients with myocardial infarction within the last 90 days.
- Patients with unstable angina or angina occurring during sexual intercourse.
- Patients with New York Heart Association Class 2 or greater heart failure in the last 6 months.
- Patients with uncontrolled arrhythmias, hypotension (<90/50mmHg), or uncontrolled hypertension.
- Patients with a stroke within the last 6 months.

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

4.4 Special warnings and special precautions for use

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

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

Serious cardiovascular events, including myocardial infarction, unstable angina pectoris, ventricular arrhythmia, strokes, and transient ischaemic attacks occurred during clinical studies of Cialis. In addition, hypertension and hypotension (including postural hypotension) were also seen infrequently in clinical trials. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors.

There is limited clinical data on the safety of Cialis in the following groups; if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician:

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

Tadalafil 10mg has been the highest dose studied in patients with mild (creatinine clearance = 51 to 80ml/min) and moderate (creatinine clearance = 31 to 50ml/min) renal failure and in patients with end-stage renal failure undergoing haemodialysis.

Priapism was not reported in clinical trials with Cialis. However, priapism has been reported with another PDE5 inhibitor. 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.

Cialis 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).

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

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

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

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

4.5 Interaction with other medicaments and other forms of interaction

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

EFFECTS OF OTHER MEDICINAL PRODUCTS ON TADALAFIL

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole, increased tadalafil AUC by 107%, relative to the AUC values for tadalafil alone (10mg dose). Although specific interactions have not been studied, some protease inhibitors, such as ritonavir and saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole and grapefruit juice, should be co-administered with caution as they would be expected to increase plasma concentrations of tadalafil. Consequently the incidence of the undesirable effects listed in section 4.8 might be increased.

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

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

EFFECTS OF TADALAFIL ON OTHER MEDICINAL PRODUCTS

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

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.

Tadalafil (10mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

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

In clinical pharmacology studies, the potential for tadalafil to augment the hypotensive effects of antihypertensive agents was examined. Major classes of antihypertensive agents were studied, including calcium channel blockers (amlodipine), angiotensin converting enzyme (ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium channel blockers, beta-blockers, and/or alpha-blockers). Tadalafil (10mg, except for studies with angiotensin II receptor blockers and amlodipine in which a 20mg dose was applied) had no clinically significant interaction with any of these classes. Tadalafil (10 and 20mg) had no clinically significant effect on blood pressure changes due to tamsulosin, an alpha-adrenergic receptor blocking agent. In patients receiving concomitant antihypertensive medications, tadalafil 20mg may induce a blood pressure decrease, which is, in general, minor and not likely to be clinically relevant. Analysis of Phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medications. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medications.

Alcohol concentrations (mean maximum blood concentration 0.08%) were not affected by co-administration with tadalafil (10mg). The effect of alcohol on cognitive function was not augmented by tadalafil (10mg) nor was the effect of alcohol on blood pressure augmented by tadalafil (20mg). In addition, no changes in tadalafil concentrations were seen 3 hours after co-administration with alcohol.

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

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

Specific interaction studies with antidiabetic agents were not conducted.

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

Cialis is expected to have no or negligible influence on the ability to drive and/or use machines. No specific studies have been performed to evaluate a potential effect. Although the frequency of reports of dizziness in placebo and tadalafil arms in clinical trials was similar, patients should be aware of how they react to Cialis, before driving or operating machinery.

4.8 Undesirable effects

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

Table 1 Very common adverse reactions (>1/10)			
System Organ Class	Adverse Reaction	Cialis 10-20mg (%) n = 724	Placebo (%) n = 379
Nervous system	Headache	14.5	5.5
Gastro-intestinal	Dyspepsia	12.3	1.8

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

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

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

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

4.9 Overdose

Single doses of up to 500mg have been given to healthy subjects, and multiple daily doses up to 100mg have been given to patients. Adverse events were similar to those seen at lower doses.

In cases of overdose, standard supportive measures should be adopted, as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOTHERAPEUTIC GROUP: Drugs used in erectile dysfunction (ATC Code G04B E).

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

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

Two clinical studies were conducted in 571 patients in an at-home setting to define the period of responsiveness to Cialis. Cialis demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 24 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. Sexual Encounter Profile (SEP) diary data collected in clinical studies supports this period of responsiveness and a statistically significant greater proportion of successful intercourse attempts associated with tadalafil treatment compared to placebo treatment up to and through the 12- to 14-hour interval following administration. In these studies patients were free to choose the time interval between dose administration and the time of sexual attempts.

Cialis administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8mmHg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6mmHg, respectively), and no significant change in heart rate. When tadalafil and certain oral antihypertensive medications (including angiotensin II receptor blockers) were assessed in drug interaction studies, tadalafil did not result in clinically significant augmentation of

the antihypertensive effects of those medications (see section 4.5, 'Interaction with other medicaments and other forms of interaction'). However, appropriate clinical advice should be given to patients regarding the possibility of a decrease in blood pressure when they are treated with antihypertensive medications. The administration of Cialis to patients who are using any form of organic nitrate is contra-indicated.

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

Two studies were conducted in men to assess the potential effect of Cialis 10mg and 20mg administered daily for 6 months on spermatogenesis. The results of these studies demonstrate no difference from placebo with respect to the proportion of men showing a 50% or greater decrease in sperm concentration. In addition, in comparison with placebo, there were no adverse effects observed with respect to mean change in sperm count, sperm morphology, or sperm motility at either dose. However, in the study of 10mg Cialis taken daily for 6 months, results showed a decrease in mean sperm concentration relative to placebo. This effect was not seen in the study where the higher dose, 20mg Cialis, was taken daily for 6 months. In addition, there was no effect on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20mg of Cialis compared to placebo. The effects of longer-term daily dosing have not been established. See also sections 4.4, 'Special warnings and special precautions for use', and 5.3, 'Preclinical safety data'.

Tadalafil at doses of 2 to 100mg has been evaluated in 16 clinical studies involving 3,250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), aetiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81% of patients reported that Cialis improved their erections as compared to 35% with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking Cialis (86%, 83% and 72% for mild, moderate and severe, respectively, as compared to 45%, 42% and 19% with placebo). In the primary efficacy studies, 75% of intercourse attempts were successful in Cialis-treated patients as compared to 32% with placebo.

5.2 Pharmacokinetic properties

ABSORPTION

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food, thus Cialis may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

DISTRIBUTION

The mean volume of distribution is approximately 63 litres, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

BIOTRANSFORMATION

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

ELIMINATION

The mean oral clearance for tadalafil is 2.5 l/h and the mean half-life is 17.5 hours in healthy subjects.

Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

LINEARITY/NON-LINEARITY

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

SPECIAL POPULATIONS

ELDERLY

Healthy elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

RENAL INSUFFICIENCY

In a clinical pharmacology study in subjects with mild (creatinine clearance 51 to 80ml/min) or moderate (creatinine clearance 31 to 50ml/min) renal impairment, tadalafil exposure (AUC) was higher than

in healthy subjects after administration of a 10mg dose. In another clinical pharmacology study in subjects with end-stage renal failure undergoing haemodialysis, the tadalafil exposure (AUC) after a 10mg dose was comparable to the exposure in healthy subjects.

There are no available data about the administration of doses higher than 10mg of tadalafil to patients with renal impairment.

HEPATIC INSUFFICIENCY

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10mg is administered.

There are no available data about the administration of doses higher than 10mg of tadalafil to patients with hepatic impairment.

PATIENTS WITH DIABETES

Tadalafil exposure (AUC) in patients with diabetes was approximately 19% lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

5.3 Preclinical safety data

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

There was no evidence of teratogenicity, embryotoxicity or foetotoxicity in rats or mice that received up to 1,000mg/kg/day. In a rat pre- and post-natal development study, the no observed effect dose was 30mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20mg dose.

There was no impairment of fertility in male and female rats. In dogs given tadalafil daily for 6 to 12 months at doses of 25mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also sections 4.4, 'Special warnings and special precautions for use', and 5.1, 'Pharmacodynamic properties'.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

TABLET CORE:

Lactose monohydrate
Croscarmellose sodium
Hydroxypropylcellulose
Microcrystalline cellulose
Sodium laurilsulfate
Magnesium stearate

FILM-COAT:

Lactose monohydrate
Hypromellose
Triacetin
Titanium dioxide [E171]
Iron oxide yellow [E172]
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PE/Aclar blisters in cartons of 4 tablets 10mg.

Aluminium/PVC/PE/Aclar blisters in cartons of 4 or 8 tablets 20mg.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Lilly ICOS Limited
25 New Street Square
London
EC4A 3LN
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/237/001: 4 x 10mg tablets

EU/1/02/237/003: 4 x 20mg tablets

EU/1/02/237/004: 8 x 20mg tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 2002

10. DATE OF (PARTIAL) REVISION OF THE TEXT

-

LEGAL CATEGORY

POM

*CIALIS (tadalafil) is a trademark of Lilly ICOS LLC.