Tadalafil

Cialis®

Lilly

1. NAME OF THE MEDICINAL PRODUCT
Tadalafil (Cialis®) 20 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 20 mg tadalafil. For the full list of excipients, see section 7.1.

3. PHARMACEUTICAL FORM
Tadalafil (Cialis®) is available as film-coated tablets for oral administration.
Tadalafil (Cialis®) is available as yellow almond-shaped film-coated tablets debossed with "C20".

4. PHARMACOLOGIC CATEGORY
Phosphodiesterase Type-5 Inhibitor

5. CLINICAL PARTICULARS

5.1 Therapeutic indications
Tadalafil (Cialis®) is indicated for the treatment of erectile dysfunction (ED).

5.2 Posology and method of administration

Dosage and Administration

Do not split Tadalafil (Cialis®) tablets; entire dose should be taken.

The recommended starting dose of Tadalafil (Cialis®) for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.

The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

Tadalafil (Cialis®) for use as needed was shown to improve erectile function compared to placebo up to 36 hours following dosing. Therefore, when advising patients on optimal use of Tadalafil (Cialis®), this should be taken into consideration.

Use with Food
Tadalafil (Cialis®) may be taken without regard to food.

Use in Specific Populations
Renal Impairment
- Creatinine clearance 30 to 50 mL/min: A starting dose of 5 mg not more than once per day is recommended, and the maximum dose is 10 mg not more than once in every 48 hours.
- Creatinine clearance less than 30 mL/min or on hemodialysis: The maximum dose is 5 mg not more than once in every 72 hours *(see section 5.4 Special Warnings and Precautions for Use).*

Hepatic Impairment
- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10 mg once per day. The use of Tadalafil (Cialis®) once per day has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised.
- Severe (Child Pugh Class C): The use of Tadalafil (Cialis®) is not recommended *(see section 5.4 Special Warnings and Precautions for Use).*

Pediatric Use
Tadalafil (Cialis®) is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

Geriatric Use
No dose adjustment is warranted based on age alone.

Concomitant Medications
Alpha-Blockers
When Tadalafil (Cialis®) is coadministered with an alpha-blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and Tadalafil (Cialis®) should be initiated at the lowest recommended dose *(see section 5.4 Special Warnings and Precautions for Use; 5.7 Undesirable effects; 6.2 Pharmacodynamics).*

CYP3A4 Inhibitors
For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of Tadalafil (Cialis®) is 10 mg, not to exceed once every 72 hours *(see section 5.4 Special Warnings and Precautions for Use; 5.7 Undesirable effects; 6.2 Pharmacodynamics).*

5.3 Contraindications
Nitrates
Administration of Tadalafil (Cialis®) to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, Tadalafil (Cialis®) was shown to potentiate the hypotensive effects of nitrates *(see section 6.2 Pharmacodynamics).*

Hypersensitivity Reactions
Tadalafil (Cialis®) is contraindicated in patients with a known serious hypersensitivity to Tadalafil (Cialis®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis *(see section 5.7 Undesirable effects).*

Concomitant Guanylate Cyclase (GC) Stimulators
Do not use Tadalafil (Cialis®) in patients who are using a GC stimulator. PDE5 inhibitors, including Tadalafil (Cialis®), may potentiate the hypotensive effects of GC stimulators.

5.4 Special warnings and special precautions for use
Evaluation of erectile dysfunction should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options. Before prescribing Tadalafil (Cialis®), it is important to note the following:

Cardiovascular
Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with the sexual activity. Therefore, treatments for erectile dysfunction, including Tadalafil (Cialis®), should not be used in men for whom sexual activity is inadvisable as a result of their underlying cardiovascular status. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and seek immediate medical attention. Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of Tadalafil (Cialis®). In such a patient, who has taken Tadalafil (Cialis®), where nitrate administration is deemed medically necessary for a life- threatening situation, at least 48 hours should have elapsed after the last dose of Tadalafil (Cialis®) before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Therefore, patients who experience anginal chest pain after taking Tadalafil (Cialis®) should seek immediate medical attention *(see section 5.3 Contraindications).*

Patients with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) can be sensitive to the action of vasodilators, including PDE5 inhibitors.

The following groups of patients with cardiovascular disease were not included in clinical safety and efficacy trials for Tadalafil (Cialis®), and therefore until further information is available, Tadalafil (Cialis®) is not recommended for the following groups of patients:
- myocardial infarction within the last 90 days
- unstable angina or angina occurring during sexual intercourse
- New York Heart Association Class 2 or greater heart failure in the last 6 months
- uncontrolled arrhythmias, hypotension (< 90/50 mmHg), or uncontrolled hypertension
- stroke within the last 6 months

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. In a clinical pharmacology study, tadalafil 20 mg resulted in a mean maximal decrease in supine blood pressure, relative to placebo, of 1.6/0.8 mmHg in healthy subjects *(see section 6.2 Pharmacodynamics).* While this effect should not be of consequence in most patients, prior to prescribing Tadalafil (Cialis®), physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

Prolonged Erection
There have been reports of prolonged erections lasting 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

Tadalafil (Cialis®) should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Effects on the Eye
Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including Tadalfil (Cialis®), and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and 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. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50.

An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies.

Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION *(see section 5.7 Undesirable Effects).*

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including Tadalafil (Cialis®), should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including Tadalafil (Cialis®), for this uncommon condition.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Sudden Hearing Loss
Physicians should advise patients to stop taking PDE5 inhibitors, including Tadalafil (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 Tadalafil (Cialis®). It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *(see section 5.7 Undesirable Effects).*

Alpha Blockers and Antihypertensives
Physicians should discuss with patients the potential for Tadalafil (Cialis®) to augment the blood- pressure-lowering effect of alpha-blockers and antihypertensive medications *(see section 5.5 Interactions with other medicinal products and other form of interactions, 6.2 Pharmacodynamics).*

Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including Tadalafil (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 *(see section 5.5 Interaction with other medicinal products and other forms of interactions, 6.2 Pharmacodynamics),* 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 antihypertensive drugs *(see section 5.2 Posology and method of administration, 5.5 Interaction with other medicinal products and other forms of interactions).*

Renal Impairment
Tadalafil (Cialis®) should be limited to 5 mg not more than once in every 72 hours in patients with creatinine clearance less than 30 mL/min or end-stage renal disease on hemodialysis. The starting dose of Tadalafil (Cialis®) in patients with creatinine clearance 30 – 50 mL/min should be 5 mg not more than once per day, and the maximum dose should be limited to 10 mg not more than once in every 48 hours.

Hepatic Impairment
In patients with mild or moderate hepatic impairment, the dose of Tadalafil (Cialis®) should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of Tadalafil (Cialis®) in this group is not recommended.

Alcohol
Patients should be made aware that both alcohol and Tadalafil (Cialis®), a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with Tadalafil (Cialis®) can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *(see section 6.2 Pharmacodynamics).*

Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)
Tadalafi (Cialis®) is metabolized predominantly by CYP3A4 in the liver. The dose of Tadalafil (Cialis®) for use as needed should be limited to 10 mg no more than once every 72 hours in patients taking potent inhibitors of CYP3A4 such as ritonavir, ketoconazole and itraconazole *(see section 5.5 Interaction with other medicinal products and other forms of interactions).*

Combination with Other PDE5 Inhibitors or Erectile Dysfunction Therapies
The safety and efficacy of combinations of Tadalafil (Cialis®) and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take Tadalafil (Cialis®) with other PDE5 inhibitors.

Effects on Bleeding
Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. Tadalafil (Cialis®) has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although Tadalafil (Cialis®) has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Counseling Patients About Sexually Transmitted Diseases
The use of Tadalafil (Cialis®) offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

5.5 Interaction with other medicinal products and other forms of interactions Potential for Pharmacodynamic Interactions with Tadalafil (Cialis®)
Nitrates - Administration of Tadalafil (Cialis®) to patients who are using any form of organic nitrate is contraindicated. In clinical pharmacology studies, Tadalafil (Cialis®) was shown to potentiate the hypotensive effects of nitrates. In a patient who has taken Tadalafil (Cialis®), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of Tadalafil (Cialis®) before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *(see section 5.2 Posology and method of administration, 5.3 Contraindications, 6.2 Pharmacodynamics).*

Alpha-Blockers – Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors including Tadalafil (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. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin. *(see section 5.2 Posology and method of administration, 5.4 Special Warnings and Precautions for Use, 6.2 Pharmacodynamics).*

Antihypertensives – PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo *(see section 5.4 Special Warnings and Precautions for Use, 6.2 Pharmacodynamics).*

Alcohol – Both alcohol and tadalafil, a PDE5 inhibitor, act as a mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g. 5 units or greater) in combination with Tadalafil (Cialis®) can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness and headache. Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations *(see section 5.4 Special Warnings and Precautions for Use, 6.2 Pharmacodynamics).*

Potential for Other Drugs to Affect Tadalafil (Cialis®)
(See section 5.2 Posology and method of administration, 5.4 Special Warnings and Precautions for Use).
Antacids - Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H_2 Antagonists (e.g. Nizatidine) - An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors – Tadalafil (Cialis®) is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

CYP3A4 (e.g.Ketoconazole) - Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone *(see section 5.2 Posology and method of administration).*

Although specific interactions have not been studied, other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure.

HIV Protease inhibitor — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in C_{max}, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single- dose exposure (AUC) by 124% with no change in C_{max}, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure *(see section 5.2 Posology and method of administration).*

Cytochrome P450 Inducers - Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure.

CYP3A4 (e.g., Rifampin) — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10- mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of Tadalafil (Cialis®) for once daily use; the magnitude of decreased efficacy is unknown.

Potential for Tadalafil (Cialis®) to Affect Other Drugs
Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.
Cytochrome P450 Substrates — Tadalafil (Cialis®) is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

CYP1A2 (e.g. Theophylline) — Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed.

CYP2C9 (e.g.Warfarin) — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.

CYP3A4 (e.g. Midazolam or Lovastatin) — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin.

P-glycoprotein (e.g. Digoxin) — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects.

5.6 Fertility, pregnancy and lactation

Pregnancy
Risk Summary
Tadalafil (Cialis®) is not indicated for use in females.

There are no data with the use of Tadalafil (Cialis®) in pregnant women to inform any drug-associated risks for adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats or mice during organogenesis at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day.

Data
Animal Data
Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given orally to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In a prenatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to tadalafil doses greater than 10 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 16 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

In another rat prenatal and postnatal development study at doses of 60, 200, and 1000 mg/kg, a reduction in postnatal survival of pups was observed. The no observed effect level (NOEL) for maternal toxicity was 200 mg/kg/day and for developmental toxicity was 30 mg/kg/day. This gives approximately 16 and 10 fold exposure multiples, respectively, of the human AUC for the MRHD of 20 mg.

Tadalafil and/or its metabolites cross the placenta, resulting in fetal exposure in rats.

Lactation
Risk Summary
Tadalafil (Cialis®) is not indicated for use in females.

There is no information on the presence of tadalafil and/or metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

5.7 Undesirable effects

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Tadalafil was administered to over 9000 men during clinical trials worldwide. In trials of Tadalafil (Cialis®) for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

In eight primary placebo-controlled clinical studies of 12 weeks duration, mean age was 59 years (range 22 to 88) and the discontinuation rate due to adverse events in patients treated with tadalafil 10 or 20 mg was 3.1%, compared to 1.4% in placebo treated patients. When taken as recommended in the placebo-controlled clinical trials, the following adverse reactions were reported (see Table 1) for Tadalafil (Cialis®) for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with Tadalafil (Cialis®) (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for Tadalafil (Cialis®) for Use as Needed for ED

Adverse Reaction	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing [a]	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

[a] The term flushing includes: facial flushing and flushing

Across placebo-controlled studies with Tadalafil (Cialis®) for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with Tadalafil (Cialis®) (2.5% of patients) *(see section 5.2 Posology and method of administration – Use in Specific Populations).*

Across all studies with any Tadalafil (Cialis®) dose, reports of changes in color vision were rare (<0.1% of patients).

The following section identifies additional, less frequent events (<2%) reported in controlled clinical trials of Tadalafil (Cialis®) for once daily use or use as needed. A causal relationship of these events to Tadalafil (Cialis®) is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and reports too imprecise to be meaningful:
Body as a Whole — asthenia, face edema, fatigue, pain, peripheral edema
Cardiovascular — angina pectoris, chest pain, hypotension, myocardial infarction, postural hypotension, palpitations, syncope, tachycardia
Digestive — abnormal liver function tests, dry mouth, dysphagia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage
Musculoskeletal — arthralgia, neck pain
Nervous — dizziness, hypesthesia, insomnia, paresthesia, somnolence, vertigo
Renal and Urinary — renal impairment
Respiratory — dyspnea, epistaxis, pharyngitis
Skin and Appendages — pruritus, rash, sweating
Ophthalmologic — blurred vision, changes in color vision, conjunctivitis (including conjunctival hyperemia), eye pain, lacrimation increase, swelling of eyelids
Otologic — sudden decrease or loss of hearing, tinnitus
Urogenital — erection increased, spontaneous penile erection

Postmarketing Experience
The following adverse reactions have been identified during post approval use of Tadalafil (Cialis®). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and Cerebrovascular – Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported post marketing in temporal association with the use of tadalafil. Most, but not all, of these patients had pre- existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of Tadalafil (Cialis®) without sexual activity. Others were reported to have occurred hours to days after the use of Tadalafil (Cialis®) and sexual activity. It is not possible to determine whether these events are related directly to Tadalafil (Cialis®), to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *(see section 5.4 Special Warnings and Precautions for Use).*

Body as a Whole – hypersensitivity reactions including rash, urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous System – migraine, seizure and seizure recurrence, transient global amnesia

Ophthalmologic — visual field defect, retinal vein occlusion, retinal artery 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 PDE5 inhibitors, including Tadalafil (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 *(see section 5.4 Special Warnings and Precautions for Use).*

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including Tadalafil (Cialis®). In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic 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 (Cialis®), to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *(see section 5.4 Special Warnings and Precautions for Use).*

Urogenital — priapism *(see section 5.4 Special Warnings and Precautions for Use).*

PPD Information Box

Technical Information:

PMS364
BLACK
PMS485
PMS143
DIE CUT

Previous Item Code *(to be destroyed)*
PA010SPPL04

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

6. PHARMACOLOGICAL PROPERTIES

6.1 Mechanism of Action
Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation.

The effect of PDE5 inhibition on cGMP concentration in the corpus cavernosum and pulmonary arteries is also observed in the smooth muscle of the prostate, the bladder and their vascular supply. The mechanism for reducing BPH symptoms has not been established.

Studies *in vitro* have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in the smooth muscle of the corpus cavernosum, prostate, and bladder as well as in vascular and visceral smooth muscle, skeletal muscle, urethra, platelets, kidney, lung, cerebellum, heart, liver, testis, seminal vesicle, and pancreas.

In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. These studies have shown that 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. Additionally, tadalafil is 700-fold more potent for PDE5 than for PDE6, which is found in the retina and is responsible for phototransduction. Tadalafil is >9,000-fold more potent for PDE5 than for PDE8, PDE9, and PDE10. Tadalafil is 14-fold more potent for PDE5 than for PDE11A1 and 40-fold more potent for PDE5 than for PDE11A4, two of the four known forms of PDE11. PDE11 is an enzyme found in human prostate, testes, skeletal muscle and in other tissues (e.g., adrenal cortex). *In vitro,* tadalafil inhibits human recombinant PDE11A1 and, to a lesser degree, PDE11A4 activities at concentrations within the therapeutic range. The physiological role and clinical consequence of PDE11 inhibition in humans have not been defined.

6.2 Pharmacodynamics
Effects on Blood Pressure
Tadalafil 20 mg administered to healthy male subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (difference in the mean maximal decrease of 1.6/0.8 mmHg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mmHg, respectively). In addition, there was no significant effect on heart rate.

Effects on Blood Pressure When Administered with Nitrates
In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of Tadalafil (Cialis®) in patients taking any form of nitrates is contraindicated *(see section 5.3 Contraindications).*

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4mg sublingual nitroglycerin (NTG) at pre-specified timepoints, following their last dose of tadalafil (2, 4, 8, 24, 48, 72, and 96 hours after tadalafil). The objective of the study was to determine when, after tadalafil dosing, no apparent blood pressure interaction was observed. In this study, a significant interaction between tadalafil and NTG was observed at each timepoint up to and including 24 hours. At 48 hours, by most hemodynamic measures, the interaction between tadalafil and NTG was not observed, although a few more tadalafil subjects compared to placebo experienced greater blood-pressure lowering at this timepoint. After 48 hours, the interaction was not detectable *(see Figure 1).*

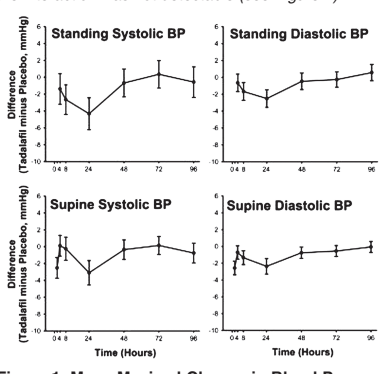

Figure 1: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, Tadalafil (Cialis®) administration with nitrates is contraindicated. In a patient who has taken Tadalafil (Cialis®), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of Tadalafil (Cialis®) before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *(see section 5.3 Contraindications).*

Effect on Blood Pressure When Administered With Alpha-Blockers
Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects *(see 5.2 Posology and method of administration, 5.4 Special Warnings and Precautions for Use).* In four studies, a single oral dose of tadalafil was administered to healthy male subjects taking daily (at least 7 days duration) an oral alpha-blocker. In two studies, a daily oral alpha-blocker (at least 7 days duration) was administered to healthy male subjects taking repeated daily doses of tadalafil.

Doxazosin —Clinical pharmacology studies were conducted with tadalafil and doxazosin, an alpha[1]- adrenergic blocker.
In the first doxazosin study, a single oral dose of tadalafil 20 mg or placebo was administered in a 2- period, crossover design to healthy subjects taking oral doxazosin 8 mg daily (N=18 subjects). Doxazosin was administered at the same time as tadalafil or placebo after a minimum of seven days of doxazosin dosing *(see Table 2 and Figure 2).*

Table 2: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg)	Tadalafil 20mg
Supine	3.6 (-1.5,8.8)
Standing	9.8 (4.1, 15.5)

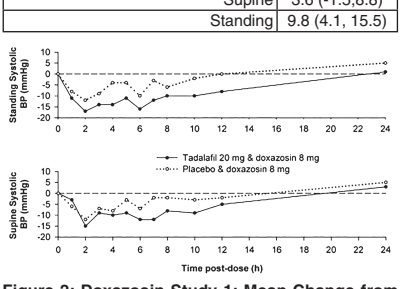

Figure 2: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo administration. Outliers were defined as subjects with a standing systolic blood pressure of <85 mmHg or a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points. There were nine and three outliers following administration of tadalafil 20 mg and placebo, respectively. Five and two subjects were outliers due to a decrease from baseline in standing systolic BP of >30 mmHg, while five and one subject were outliers due to standing systolic BP <85 mmHg following tadalafil and placebo, respectively. Severe adverse events potentially related to blood-pressure effects were assessed. No such events were reported following placebo. Two such events were reported following administration of tadalafil. Vertigo was reported in one subject that began 7 hours after dosing and lasted about 5 days. This subject previously experienced a mild episode of vertigo on doxazosin and placebo. Dizziness was reported in another subject that began 25 minutes after dosing and lasted 1 day. No syncope was reported.

In the second doxazosin study, a single oral dose of tadalafil 20 mg was administered to healthy subjects taking oral doxazosin, either 4 or 8 mg daily. The study (N=72 subjects) was conducted in three parts, each a 3-period crossover.

In part A (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 a.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part B (N=24), subjects were titrated to doxazosin 4 mg administered daily at 8 p.m. Tadalafil was administered at either 8 a.m., 4 p.m., or 8 p.m. There was no placebo control.

In part C (N=24), subjects were titrated to doxazosin 8 mg administered daily at 8 a.m. In this part, tadalafil or placebo were administered at either 8 a.m. or 8 p.m.

The placebo-subtracted mean maximal decreases in systolic blood pressure over a 12-hour period after dosing in the placebo-controlled portion of the study (part C) are shown in Table 3 and Figure 3.

Table 3: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg)	Tadalafil 20mg at 8 a.m.	Tadalafil 20 mg at 8 p.m.
Ambulatory Blood-Pressure Monitoring (ABPM)	7	8

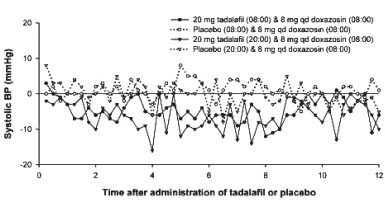

Figure 3: Doxazosin Study 2 (Part C): Mean Change from Time-Matched Baseline in Systolic Blood Pressure

Blood pressure was measured by ABPM every 15 to 30 minutes for up to 36 hours after tadalafil or placebo. Subjects were categorized as outliers if one or more systolic blood pressure readings of <85 mmHg were recorded or one or more decreases in systolic blood pressure of >30 mmHg from a time- matched baseline occurred during the analysis interval.

Of the 24 subjects in part C, 16 subjects were categorized as outliers following administration of tadalafil and 6 subjects were categorized as outliers following placebo during the 24-hour period after 8 a.m. dosing of tadalafil or placebo. Of these, 5 and 2 were outliers due to systolic BP <85 mmHg, while 15 and 4 were outliers due to a decrease from baseline in systolic BP of >30 mmHg following tadalafil and placebo, respectively.

During the 24-hour period after 8 p.m. dosing, 17 subjects were categorized as outliers following administration of tadalafil and 7 subjects following placebo. Of these, 10 and 2 subjects were outliers due to systolic BP <85 mmHg, while 15 and 5 subjects were outliers due to a decrease from baseline in systolic BP of >30 mmHg, following tadalafil and placebo, respectively.

Some additional subjects in both the tadalafil and placebo groups were categorized as outliers in the period beyond 24 hours.

Severe adverse events potentially related to blood-pressure effects were assessed. In the study (N=72 subjects), 2 such events were reported following administration of tadalafil (symptomatic hypotension in one subject that began 10 hours after dosing and lasted approximately 1 hour, and dizziness in another subject that began 11 hours after dosing and lasted 2 minutes). No such events were reported following placebo. In the period prior to tadalafil dosing, one severe event (dizziness) was reported in a subject during the doxazosin run-in phase.

Tamsulosin — In tamsulosin study, a single oral dose of tadalafil 10, 20 mg, or placebo was administered in a 3 period, crossover design to healthy subjects taking 0.4 mg once per day tamsulosin, a selective alpha[1A]- adrenergic blocker (N=18 subjects). Tadalafil or placebo was administered 2 hours after tamsulosin following a minimum of seven days of tamsulosin dosing.

Table 4: Tamsulosin (0.4 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg)	Tadalafil 10mg	Tadalafil 20mg
Supine	3.2 (-2.3, 8.6)	3.2 (-2.3, 8.7)
Standing	1.7 (-4.7, 8.1)	2.3 (-4.1, 8.7)

Blood pressure was measured manually at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after tadalafil or placebo dosing. There were 2, 2, and 1 outliers (subjects with a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points) following administration of tadalafil 10 mg, 20 mg, and placebo, respectively. There were no subjects with a standing systolic blood pressure <85 mmHg. No severe adverse events potentially related to blood-pressure effects were reported. No syncope was reported.

Alfuzosin — A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]- adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.

Table 5: Alfuzosin (10 mg/day) Study: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

Placebo-subtracted mean maximal decrease in systolic blood pressure (mmHg)	Tadalafil 20 mg
Supine	2.2 (-0.9, -5.2)
Standing	4.4 (-0.2, 8.9)

Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing.

There was 1 outlier (subject with a standing systolic blood pressure <85 mmHg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mmHg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

Effects on Blood Pressure When Administered with Antihypertensives
Amlodipine — A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg.

There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mmHg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

Angiotensin II receptor blockers (with and without other antihypertensives) — A study was conducted to assess the interaction of angiotensin II receptor blockers and tadalafil 20 mg. Subjects in the study were taking any marketed angiotensin II receptor blocker, either alone, as a component of a combination product, or as part of a multiple antihypertensive regimen. Following dosing, ambulatory measurements of blood pressure revealed differences between tadalafil and placebo of 8/4 mmHg in systolic/diastolic blood pressure.

Bendrofluazide — A study was conducted to assess the interaction of bendrofluazide (2.5 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking bendrofluazide was 6/4 mmHg, compared to placebo.

Enalapril — A study was conducted to assess the interaction of enalapril (10 to 20 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking enalapril was 4/1 mmHg, compared to placebo.

Metoprolol — A study was conducted to assess the interaction of sustained-release metoprolol (25 to 200 mg daily) and tadalafil 10 mg. Following dosing, the mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking metoprolol was 5/3 mmHg, compared to placebo.

Effects on Blood Pressure When Administered with Alcohol
Alcohol and PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. The interaction of tadalafil with alcohol was evaluated in 3 clinical pharmacology studies. In 2 of these, alcohol was administered at a dose of 0.7 g/kg, which is equivalent to approximately 6 ounces of 80-proof vodka in an 80-kg male, and tadalafil was administered at a dose of 10 mg in one study and 20 mg in another. In both these studies, all patients imbibed the entire alcohol dose within 10 minutes of starting. In one of these two studies, blood alcohol levels 0.08% were confirmed. In these two studies, more patients had clinically significant decreases in blood pressure on the combination of tadalafil and alcohol as compared to alcohol alone. Some subjects reported postural dizziness, and orthostatic hypotension was observed in some subjects. When tadalafil 20 mg was administered with a lower dose of alcohol (0.6 g/kg, which is equivalent to approximately 4 ounces of 80-proof vodka, administered in less than 10 minutes), orthostatic hypotension was not observed, dizziness occurred with similar frequency to alcohol alone, and the hypotensive effects of alcohol were not potentiated.

Tadalafil did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Effects on Exercise Stress Testing
The effects of tadalafil on cardiac function, hemodynamics and exercise tolerance were investigated in a single clinical pharmacology study. In this blinded crossover trial, 23 subjects with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time was 3 seconds (tadalafil 10 mg minus placebo), which represented no clinically meaningful difference. Further statistical analysis demonstrated that tadalafil was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some subjects who received tadalafil followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed, consistent with the augmentation by tadalafil of the blood-pressure-lowering effects of nitrates.

Effects on Vision
Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupilometry. Across all clinical studies with Tadalafil (Cialis®), reports of changes in color vision were rare (<0.1% of patients).

Effects on Sperm Characteristics
Three studies were conducted in men to assess the potential effect on sperm characteristics 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 9 months, results showed a decrease in mean sperm concentrations relative to placebo, although these differences were not clinically meaningful. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. In addition there was no adverse effect on mean concentrations of reproductive hormones, testosterone, luteinizing hormone or follicle stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo.

Effects on Cardiac Electrophysiology
The effect of a single 100-mg dose of tadalafil on the QT interval was evaluated at the time of peak tadalafil concentration in a randomized, double-blinded, placebo, and active (intravenous ibutilide) - controlled crossover study in 90 healthy males aged 18 to 53 years. The mean change in QTc (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 milliseconds (two-sided 90% CI=1.9, 5.1). The mean change in QTc (Individual QT correction) for tadalafil, relative to placebo, was 2.8 milliseconds (two-sided 90% CI=1.2, 4.4). A 100-mg dose of tadalafil (5 times the highest recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. In this study, the mean increase in heart rate associated with a 100-mg dose of tadalafil compared to placebo was 3.1 beats per minute.

6.3 Pharmacokinetics
Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once per day dosing and exposure is approximately 1.6-fold greater than after a single dose. Mean tadalafil concentrations measured after the administration of a single oral dose of 20 mg and single and once daily multiple doses of 5 mg, from a separate study, (*see* Figure 4) to healthy male subjects are depicted in Figure 4.

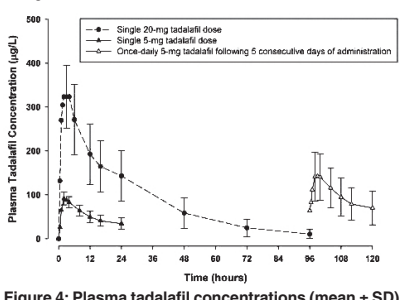

Figure 4: Plasma tadalafil concentrations (mean ± SD) following a single 20-mg tadalafil dose and single and once daily multiple doses of 5 mg

Absorption – After single oral-dose administration, the maximum observed plasma concentration (C_{max}) of tadalafil is achieved between 30 minutes and 60 hours (median of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.
The rate and extent of absorption of tadalafil are not influenced by food, this Tadalafil (Cialis®) may be taken with or without food

Distribution – The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.
Less than 0.0005% If the administered dose appeared in the semen of healthy subjects.

Excretion – 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 metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Geriatric – Healthy male elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on C_{max} relative to that observed in healthy subjects 19 to 45 years age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medication in some older individuals should be considered *(see section 5.2 Posology and method of administration – Use in Specific Populations).*

Patients with Diabetes Mellitus – In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and C_{max} was 5% lower than that observed in healthy subjects. No dose adjustments was warranted.

Patients with BPH – In patients with BPH following single and multiple-doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and C_{max}) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.
There were no treatment-related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

7. PHARMACEUTICAL PARTICULARS

7.1 List of Excipients
Lactose monohydrate
Croscarmellose sodium
Hydroxypropyl cellulose
Microcrystalline cellulose
Sodium laurilsulfate
Magnesium stearate

7.2 Incompatabilities
Not applicable

7.3 Shelf life
3 years

7.4 Special precautions for storage
Store at temperatures not exceeding 30°C.

8. Availability
Tadalafil (Cialis®) 20 mg Alu/Alu Blister Pack of 1 tablet (Box of 2 tablets).

9. Manufactured by:
Lilly del Caribe, Inc.
Km 12.6, 65th Infantry Road, Carolina, Puerto Rico, PR00985, United States of America

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

10. Imported and Distributed by:
Zuellig Pharma Corporation
Km 14 West Service Rd., South Superhighway corner Edison Ave. Sun Valley, Parañaque City, Philippines

11. Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

12. ADR Reporting Statement:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction

13. Registration Number
DR-XY44985

14. Date of First Authorization
28 March 2003

15. Date of Revision of Package Insert
22 Sep 2023
USPI 20180215

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