HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CIALIS safely and effectively. See full prescribing information for CIALIS.

CIALIS (tadalafil) tablets, for oral use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Indications and Usage, Limitation of Use (1.4)	10/2013
Dosage and Administration, CIALIS for Once Daily Use for Benign Prostatic Hyperplasia (2.3)	10/2013
Warnings and Precautions, Effects on the Eye (5.4)	04/2014

----------INDICATIONS AND USAGE----------

CIALIS® is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of:
- erectile dysfunction (ED) (1.1)
- the signs and symptoms of benign prostatic hyperplasia (BPH) (1.2)
- ED and the signs and symptoms of BPH (ED/BPH) (1.3)

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks (1.4).

----------DOSAGE AND ADMINISTRATION----------
- *CIALIS for use as needed:*
- ED: Starting dose: 10 mg as needed prior to sexual activity. Increase to 20 mg or decrease to 5 mg based upon efficacy/tolerability. Improves erectile function compared to placebo up to 36 hours post dose. Not to be taken more than once per day (2.1).
- *CIALIS for once daily use:*
- ED: 2.5 mg taken once daily, without regard to timing of sexual activity. May increase to 5 mg based upon efficacy and tolerability (2.2).
- BPH: 5 mg, taken at approximately the same time every day (2.3)
- ED and BPH: 5 mg, taken at approximately the same time every day (2.3, 2.4)
- CIALIS may be taken without regard to food (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 2.5 mg, 5 mg, 10 mg, 20 mg (3).

----------CONTRAINDICATIONS----------
- Administration of CIALIS to patients using any form of organic nitrate is contraindicated. CIALIS was shown to potentiate the hypotensive effect of nitrates (4.1).
- History of known serious hypersensitivity reaction to CIALIS or ADCIRCA® (4.2).

----------WARNINGS AND PRECAUTIONS----------
- Patients should not use CIALIS if sex is inadvisable due to cardiovascular status (5.1).
- Use of CIALIS with alpha-blockers, antihypertensives or substantial amounts of alcohol (≥5 units) may lead to hypotension (5.6, 5.9).
- CIALIS is not recommended in combination with alpha-blockers for the treatment of BPH because efficacy of the combination has not been adequately studied and because of the risk of blood pressure lowering. Caution is advised when CIALIS is used as a treatment for ED in men taking alpha-blockers. (2.7, 5.6, 7.1, 12.2)
- Patients should seek emergency treatment if an erection lasts >4 hours. Use CIALIS with caution in patients predisposed to priapism (5.3).
- Patients should stop CIALIS and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). CIALIS should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION (5.4, 6.2).
- Patients should stop CIALIS and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5).
- Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms (5.14).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥2%) include headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- CIALIS can potentiate the hypotensive effects of nitrates, alpha-blockers, antihypertensives or alcohol (7.1).
- CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase CIALIS exposure (2.7, 5.10, 7.2) requiring dose adjustment:
  - CIALIS for use as needed: no more than 10 mg every 72 hours
  - CIALIS for once daily use: dose not to exceed 2.5 mg
- CYP3A4 inducers (e.g. rifampin) decrease CIALIS exposure (7.2).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic Impairment (2.6, 5.8, 8.6):
- Mild or Moderate: Dosage adjustment may be needed.
- Severe: Use is not recommended.

Renal Impairment (2.6, 5.7, 8.7):
- Patients with creatinine clearance 30 to 50 mL/min: Dosage adjustment may be needed.
- Patients with creatinine clearance less than 30 mL/min or on hemodialysis: For use as needed: Dose should not exceed 5 mg every 72 hours. Once daily use is not recommended.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Erectile Dysfunction

CIALIS® is indicated for the treatment of erectile dysfunction (ED).

1.2 Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

1.3 Erectile Dysfunction and Benign Prostatic Hyperplasia

CIALIS is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

1.4 Limitation of Use

If CIALIS is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of CIALIS decreases from 4 weeks until 26 weeks, and the incremental benefit of CIALIS beyond 26 weeks is unknown *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

Do not split CIALIS tablets; entire dose should be taken.

2.1 CIALIS for Use as Needed for Erectile Dysfunction

- The recommended starting dose of 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.
- 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 CIALIS, this should be taken into consideration.

2.2 CIALIS for Once Daily Use for Erectile Dysfunction

- The recommended starting dose of CIALIS for once daily use is 2.5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.
- The CIALIS dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

2.3 CIALIS for Once Daily Use for Benign Prostatic Hyperplasia

- The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day.
- When therapy for BPH is initiated with CIALIS and finasteride, the recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks.

2.4 CIALIS for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of CIALIS for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

2.5 Use with Food

CIALIS may be taken without regard to food.

2.6 Use in Specific Populations

Renal Impairment

CIALIS for Use as Needed

- 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 Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

Erectile Dysfunction

- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Benign Prostatic Hyperplasia and Erectile Dysfunction/Benign Prostatic Hyperplasia

- Creatinine clearance 30 to 50 mL/min: A starting dose of 2.5 mg is recommended. An increase to 5 mg may be considered based on individual response.
- Creatinine clearance less than 30 mL/min or on hemodialysis: CIALIS for once daily use is not recommended *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Hepatic Impairment

CIALIS for Use as Needed

- Mild or moderate (Child Pugh Class A or B): The dose should not exceed 10 mg once per day. The use of 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 CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

- Mild or moderate (Child Pugh Class A or B): CIALIS for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of CIALIS is not recommended *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.6)]*.

2.7 Concomitant Medications

Nitrates

Concomitant use of nitrates in any form is contraindicated *[see Contraindications (4.1)]*.

Alpha-Blockers

ED — When 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 CIALIS should be initiated at the lowest recommended dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

BPH — CIALIS is not recommended for use in combination with alpha-blockers for the treatment of BPH *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

CYP3A4 Inhibitors

CIALIS for Use as Needed — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of CIALIS is 10 mg, not to exceed once every 72 hours *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

CIALIS for Once Daily Use — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose is 2.5 mg *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow:
2.5 mg tablets debossed with “C 2 1/2”
5 mg tablets debossed with “C 5”
10 mg tablets debossed with “C 10”
20 mg tablets debossed with “C 20”

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of CIALIS to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates *[see Clinical Pharmacology (12.2)]*.

4.2 Hypersensitivity Reactions

CIALIS is contraindicated in patients with a known serious hypersensitivity to tadalafil (CIALIS or ADCIRCA®). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

Evaluation of erectile dysfunction and BPH should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing CIALIS, it is important to note the following:

5.1 Cardiovascular

Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including 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 CIALIS. In such a patient, who has taken 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 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 CIALIS should seek immediate medical attention. *[see Contraindications (4.1) and Patient Counseling Information (17.1)]*.

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 CIALIS, and therefore until further information is available, 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 mm Hg), 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 mm Hg in healthy subjects *[see Clinical Pharmacology (12.2)]*. While this effect should not be of consequence in most patients, prior to prescribing 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.

5.2 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should be aware that CIALIS for once daily use provides continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, anti-hypertensives and potent inhibitors of CYP3A4) and with substantial consumption of alcohol *[see Drug Interactions (7.1, 7.2, 7.3)]*.

5.3 Prolonged Erection

There have been rare reports of prolonged erections greater than 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.

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).

5.4 Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including 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 study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. From this information, it is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors *[see Adverse Reactions (6.2)]*.

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 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 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.

5.5 Sudden Hearing Loss

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 Reactions (6.1, 6.2)]*.

5.6 Alpha-blockers and Antihypertensives

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

Caution is advised when PDE5 inhibitors are coadministered with alpha-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 *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

ED

- 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 Dosage and Administration (2.7) and Drug Interactions (7.1)].

BPH

- The efficacy of the coadministration of an alpha-blocker and CIALIS for the treatment of BPH has not been adequately studied, and due to the potential vasodilatory effects of combined use resulting in blood pressure lowering, the combination of CIALIS and alpha-blockers is not recommended for the treatment of BPH. *[see Dosage and Administration (2.7), Drug Interactions (7.1), and Clinical Pharmacology (12.2.)]*.
- Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting CIALIS for once daily use for the treatment of BPH.

5.7 Renal Impairment

CIALIS for Use as Needed

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 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. *[see Use in Specific Populations (8.7)]*.

CIALIS for Once Daily Use

ED

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min *[see Use in Specific Populations (8.7)]*.

BPH and ED/BPH

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, CIALIS for once daily use is not recommended in patients with creatinine clearance less than 30 mL/min. In patients with creatinine clearance 30 – 50 mL/min, start dosing at 2.5 mg once daily, and increase the dose to 5 mg once daily based upon individual response *[see Dosage and Administration (2.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.8 Hepatic Impairment

CIALIS for Use as Needed

In patients with mild or moderate hepatic impairment, the dose of CIALIS should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

CIALIS for Once Daily Use

CIALIS for once daily use has not been extensively evaluated in patients with mild or moderate hepatic impairment. Therefore, caution is advised if CIALIS for once daily use is prescribed to these patients. Because of insufficient information in patients with severe hepatic impairment, use of CIALIS in this group is not recommended *[see Use in Specific Populations (8.6)]*.

5.9 Alcohol

Patients should be made aware that both alcohol and 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 CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Clinical Pharmacology (12.2)]*.

5.10 Concomitant Use of Potent Inhibitors of Cytochrome P450 3A4 (CYP3A4)

CIALIS is metabolized predominantly by CYP3A4 in the liver. The dose of 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 Drug Interactions (7.2)]*. In patients taking potent inhibitors of CYP3A4 and CIALIS for once daily use, the maximum recommended dose is 2.5 mg *[see Dosage and Administration (2.7)]*.

5.11 Combination With Other PDE5 Inhibitors or Erectile Dysfunction Therapies

The safety and efficacy of combinations of CIALIS and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take CIALIS with other PDE5 inhibitors, including ADCIRCA.

5.12 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. CIALIS has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although 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.

5.13 Counseling Patients About Sexually Transmitted Diseases

The use of 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.

5.14 Consideration of Other Urological Conditions Prior to Initiating Treatment for BPH

Prior to initiating treatment with CIALIS for BPH, consideration should be given to other urological conditions that may cause similar symptoms. In addition, prostate cancer and BPH may coexist.

6 ADVERSE REACTIONS

6.1 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 CIALIS for once daily use, a total of 1434, 905, and 115 were treated for at least 6 months, 1 year, and 2 years, respectively. For CIALIS for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

CIALIS for Use as Needed for ED

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 CIALIS for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with 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 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

CIALIS for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 or 24 weeks duration, mean age was 58 years (range 21 to 82) and the discontinuation rate due to adverse events in patients treated with tadalafil was 4.1%, compared to 2.8% in placebo-treated patients.

The following adverse reactions were reported (*see* Table 2) in clinical trials of 12 weeks duration:

Table 2: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in the Three Primary Placebo-Controlled Phase 3 Studies of 12 weeks Treatment Duration (Including a Study in Patients with Diabetes) for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=248)	Tadalafil 2.5 mg (N=196)	Tadalafil 5 mg (N=304)
Headache	5%	3%	6%
Dyspepsia	2%	4%	5%
Nasopharyngitis	4%	4%	3%
Back pain	1%	3%	3%
Upper respiratory tract infection	1%	3%	3%
Flushing	1%	1%	3%
Myalgia	1%	2%	2%
Cough	0%	4%	2%
Diarrhea	0%	1%	2%
Nasal congestion	0%	2%	2%
Pain in extremity	0%	1%	2%
Urinary tract infection	0%	2%	0%
Gastroesophageal reflux disease	0%	2%	1%
Abdominal pain	0%	2%	1%

The following adverse reactions were reported (*see* Table 3) over 24 weeks treatment duration in one placebo-controlled clinical study:

Table 3: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS for Once Daily Use (2.5 or 5 mg) and More Frequent on Drug than Placebo in One Placebo-Controlled Clinical Study of 24 Weeks Treatment Duration for CIALIS for Once Daily Use for ED

Adverse Reaction	Placebo (N=94)	Tadalafil 2.5 mg (N=96)	Tadalafil 5 mg (N=97)
Nasopharyngitis	5%	6%	6%
Gastroenteritis	2%	3%	5%
Back pain	3%	5%	2%
Upper respiratory tract infection	0%	3%	4%
Dyspepsia	1%	4%	1%
Gastroesophageal reflux disease	0%	3%	2%

Myalgia	2%	4%	1%
Hypertension	0%	1%	3%
Nasal congestion	0%	0%	4%

CIALIS for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, two in patients with BPH and one in patients with ED and BPH, the mean age was 63 years (range 44 to 93) and the discontinuation rate due to adverse events in patients treated with tadalafil was 3.6% compared to 1.6% in placebo-treated patients. Adverse reactions leading to discontinuation reported by at least 2 patients treated with tadalafil included headache, upper abdominal pain, and myalgia. The following adverse reactions were reported (*see* Table 4).

Table 4: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with CIALIS for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in Three Placebo-Controlled Clinical Studies of 12 Weeks Treatment Duration, including Two Studies for CIALIS for Once Daily Use for BPH and One Study for ED and BPH

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=581)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.4%
Nasopharyngitis	1.6%	2.1%
Diarrhea	1.0%	1.4%
Pain in extremity	0.0%	1.4%
Myalgia	0.3%	1.2%
Dizziness	0.5%	1.0%

Additional, less frequent adverse reactions (<1%) reported in the controlled clinical trials of CIALIS for BPH or ED and BPH included: gastroesophageal reflux disease, upper abdominal pain, nausea, vomiting, arthralgia, and muscle spasm.

Back pain or myalgia was reported at incidence rates described in Tables 1 through 4. In tadalafil clinical pharmacology trials, back pain or myalgia generally occurred 12 to 24 hours after dosing and typically resolved within 48 hours. The back pain/myalgia associated with tadalafil treatment was characterized by diffuse bilateral lower lumbar, gluteal, thigh, or thoracolumbar muscular discomfort and was exacerbated by recumbency. In general, pain was reported as mild or moderate in severity and resolved without medical treatment, but severe back pain was reported with a low frequency (<5% of all reports). When medical treatment was necessary, acetaminophen or non-steroidal anti-inflammatory drugs were generally effective; however, in a small percentage of subjects who required treatment, a mild narcotic (e.g., codeine) was used. Overall, approximately 0.5% of all subjects treated with CIALIS for on demand use discontinued treatment as a consequence of back pain/myalgia. In the 1-year open label extension study, back pain and myalgia were reported in 5.5% and 1.3% of patients, respectively. Diagnostic testing, including measures for inflammation, muscle injury, or renal damage revealed no evidence of medically significant underlying pathology. Incidence rates for CIALIS for once daily use for ED, BPH and BPH/ED are described in Tables 2, 3 and 4. In studies of CIALIS for once daily use, adverse reactions of back pain and myalgia were generally mild or moderate with a discontinuation rate of <1% across all indications.

Across all studies with any 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 CIALIS for once daily use or use as needed. A causal relationship of these events to 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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of 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 postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting 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 CIALIS without sexual activity. Others were reported to have occurred hours to days after the use of CIALIS and sexual activity. It is not possible to determine whether these events are related directly to CIALIS, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

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

Nervous — 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 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 *[see Warnings and Precautions (5.4)]*.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including 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 CIALIS, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions (5.5)]*.

Urogenital — priapism *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with CIALIS

Nitrates — Administration of CIALIS to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, CIALIS was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Dosage and Administration (2.7), Contraindications (4.1), and Clinical Pharmacology (12.2)]*.

Alpha-Blockers — Caution is advised when PDE5 inhibitors are coadministered with alpha-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. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, tamsulosin or alfuzosin. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), and Clinical Pharmacology (12.2)]*.

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 Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*.

Alcohol — Both alcohol and tadalafil, 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. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with 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 Warnings and Precautions (5.9) and Clinical Pharmacology (12.2)]*.

7.2 Potential for Other Drugs to Affect CIALIS

[See Dosage and Administration (2.7) and Warnings and Precautions (5.10)].

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 — 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 Dosage and Administration (2.7)]*.

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 Dosage and Administration (2.7)]*.

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 CIALIS for once daily use; the magnitude of decreased efficacy is unknown.

7.3 Potential for CIALIS to Affect Other Drugs

Aspirin — Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates — 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B — CIALIS (tadalafil) is not indicated for use in women. There are no adequate and well controlled studies of CIALIS use in pregnant women.

Risk Summary — Based on animal data, CIALIS is not predicted to increase the risk of adverse developmental abnormalities in humans.

Animal Data — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at exposures up to 11 times the maximum recommended human dose (MRHD) of 20 mg/day during organogenesis. In one of two perinatal/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 a 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.

8.3 Nursing Mothers

CIALIS is not indicated for use in women. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma.

8.4 Pediatric Use

CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

8.5 Geriatric Use

Of the total number of subjects in ED clinical studies of tadalafil, approximately 25 percent were 65 and over, while approximately 3 percent were 75 and over. Of the total number of subjects in BPH clinical studies of tadalafil (including the ED/BPH study), approximately 40 percent were over 65, while approximately 10 percent were 75 and over. In these clinical trials, no overall differences in efficacy or safety were observed between older (>65 and ≥75 years of age) and younger subjects (≤65 years of age). Therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered. *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

In clinical pharmacology studies, tadalafil exposure (AUC) in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) was comparable to exposure in healthy subjects when a dose of 10 mg was administered. There are no available data for doses higher than 10 mg of tadalafil in patients with hepatic impairment. Insufficient data are available for subjects with severe hepatic impairment (Child-Pugh Class C). *[see Dosage and Administration (2.6) and Warnings and Precautions (5.8)]*.

8.7 Renal Impairment

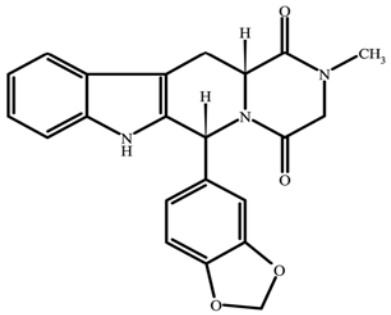
In clinical pharmacology studies using single-dose tadalafil (5 to 10 mg), tadalafil exposure (AUC) doubled in subjects with creatinine clearance 30 to 80 mL/min. In subjects with end-stage renal disease on hemodialysis, there was a two-fold increase in C_{max} and 2.7- to 4.8-fold increase in AUC following single-dose administration of 10 or 20 mg tadalafil. Exposure to total methylcatechol (unconjugated plus glucuronide) was 2- to 4-fold higher in subjects with renal impairment, compared to those with normal renal function. Hemodialysis (performed between 24 and 30 hours post-dose) contributed negligibly to tadalafil or metabolite elimination. In a clinical pharmacology study (N=28) at a dose of 10 mg, back pain was reported as a limiting adverse event in male patients with creatinine clearance 30 to 50 mL/min. At a dose of 5 mg, the incidence and severity of back pain was not significantly different than in the general population. In patients on hemodialysis taking 10- or 20-mg tadalafil, there were no reported cases of back pain. *[see Dosage and Administration (2.6) and Warnings and Precautions (5.7)]*.

10 OVERDOSAGE

Single doses 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.

11 DESCRIPTION

CIALIS (tadalafil) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:



The chemical designation 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)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

CIALIS is available as almond-shaped tablets for oral administration. Each tablet contains 2.5, 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 mm Hg, respectively) and in standing systolic and diastolic blood pressure (difference in the mean maximal decrease of 0.2/4.6 mm Hg, 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 CIALIS in patients taking any form of nitrates is contraindicated *[see Contraindications (4.1)]*.

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 0.4 mg 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).

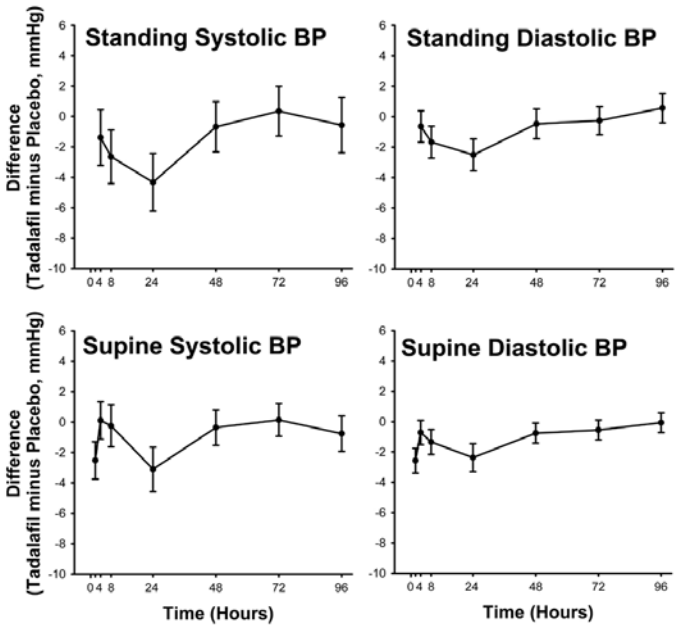


Figure 1: Mean Maximal Change in Blood Pressure (Tadalafil Minus Placebo, Point Estimate with 90% CI) in Response to Sublingual Nitroglycerin at 2 (Supine Only), 4, 8, 24, 48, 72, and 96 Hours after the Last Dose of Tadalafil 20 mg or Placebo

Therefore, CIALIS administration with nitrates is contraindicated. In a patient who has taken CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1)]*.

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 Dosage and Administration (2.7) and Warnings and Precautions (5.6)]*. 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 — Three 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 5 and Figure 2).

Table 5: Doxazosin (8 mg/day) Study 1: Mean Maximal Decrease (95% CI) in Systolic Blood Pressure

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

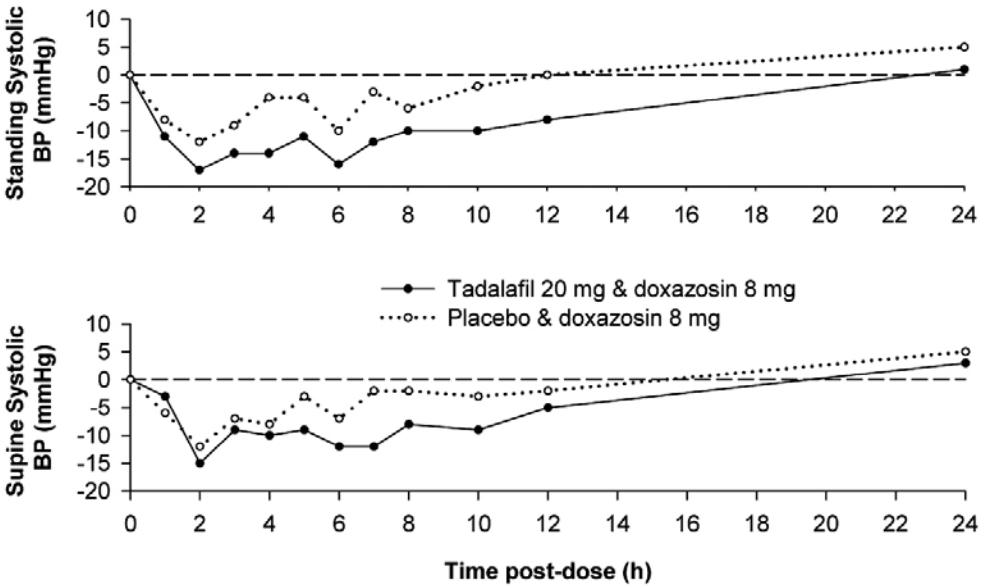


Figure 2: Doxazosin Study 1: Mean Change from Baseline in Systolic Blood Pressure

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 mm Hg or a decrease from baseline in standing systolic blood pressure of >30 mm Hg 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 mm Hg, while five and one subject were outliers due to standing systolic BP <85 mm Hg 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 6 and Figure 3.

Table 6: Doxazosin (8 mg/day) Study 2 (Part C): Mean Maximal Decrease in Systolic Blood Pressure

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

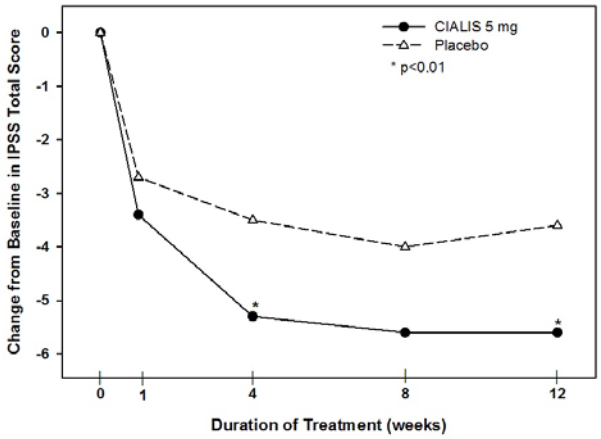


Figure 6: Mean IPSS Changes in BPH Patients by Visit in Study K

In Study J, the effect of CIALIS 5 mg once daily on maximum urinary flow rate (Q_{max}) was evaluated as a secondary efficacy endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

In Study K, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.1 mL/sec); however, these changes were not significantly different between groups.

Efficacy Results in Patients with BPH initiating CIALIS and Finasteride – CIALIS for once daily use initiated together with finasteride was shown to be effective in treating the signs and symptoms of BPH in men with an enlarged prostate (>30 cc) for up to 26 weeks. This additional double-blinded, parallel-design study of 26 weeks duration randomized 696 men to initiate either CIALIS 5 mg with finasteride 5 mg or placebo with finasteride 5 mg. The study population had a mean age of 64 years (range 46-86). Patients with multiple co-morbid conditions such as erectile dysfunction, diabetes mellitus, hypertension, and other cardiovascular disease were included.

CIALIS with finasteride demonstrated statistically significant improvement in the signs and symptoms of BPH compared to placebo with finasteride, as measured by the total IPSS at 12 weeks, the primary study endpoint (*see* Table 20). Key secondary endpoints demonstrated improvement in total IPSS starting at the first scheduled observation at week 4 (CIALIS -4.0, placebo -2.3: p<.001) and the score remained decreased through 26 weeks (CIALIS -5.5, placebo -4.5; p=.022). However, the magnitude of the treatment difference between placebo/finasteride and CIALIS/finasteride decreased from 1.7 points at Week 4 to 1.0 point at Week 26, as shown in Table 20 and in Figure 7. The incremental benefit of CIALIS beyond 26 weeks is unknown.

Table 20: Mean Total IPSS Changes in BPH Patients in a CIALIS for Once Daily Use Study Together with Finasteride

		Placebo and finasteride 5 mg		CIALIS 5mg and finasteride 5 mg	Treatment difference	
	n	(N=350)[a]	n	(N=345)[a]		p-value[b]
Total Symptom Score (IPSS)						
Baseline[c]	349	17.4	344	17.1		
Change from Baseline to Week 4[b]	340	-2.3	330	-4.0	-1.7	<.001
Change from Baseline to Week 12[b]	318	-3.8	317	-5.2	-1.4	.001
Change from Baseline to Week 26[b]	295	-4.5	308	-5.5	-1.0	.022

[a] Overall ITT population.

[b] Mixed model for repeated measurements.

[c] Unadjusted mean.

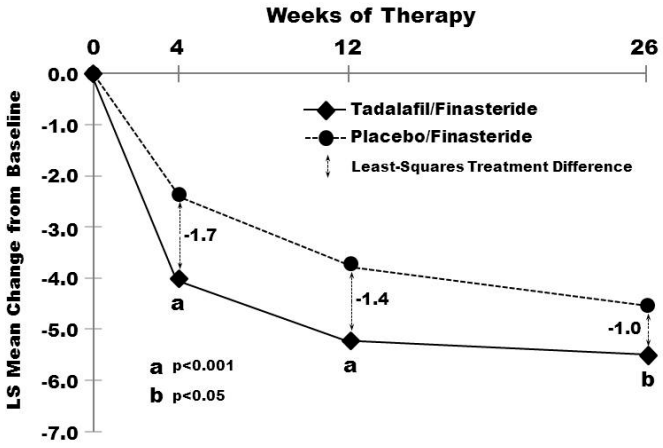


Figure 7: Mean Total IPSS Changes By Visit in BPH Patients Taking CIALIS for Once Daily Use Together With Finasteride

In the 404 patients who had both ED and BPH at baseline, changes in erectile function were assessed as key secondary endpoints using the EF domain of the IIEF questionnaire. CIALIS with finasteride (N=203) was compared to placebo with finasteride (N=201). A statistically significant improvement from baseline (CIALIS/finasteride 13.7, placebo/finasteride 15.1) was observed at week 4 (CIALIS/finasteride 3.7, placebo/finasteride -1.1; p<.001), week 12 (CIALIS/finasteride 4.7, placebo/finasteride 0.6; p<.001), and week 26 (CIALIS/finasteride 4.7, placebo/finasteride 0.0; p<.001).

14.4 CIALIS 5 mg for Once Daily Use for ED and BPH

The efficacy and safety of CIALIS for once daily use for the treatment of ED, and the signs and symptoms of BPH, in patients with both conditions was evaluated in one placebo-controlled, multinational, double-blind, parallel-arm study which randomized 606 patients to receive either CIALIS 2.5 mg, 5 mg, for once daily use or placebo. ED severity ranged from mild to severe and BPH severity ranged from moderate to severe. The full study population had a mean age of 63 years (range 45 to 83) and was 93% White, 4% Black, 3% other races; 16% were of Hispanic ethnicity. Patients with multiple co-morbid conditions such as diabetes mellitus, hypertension, and other cardiovascular disease were included.

In this study, the co-primary endpoints were total IPSS and the Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF). One of the key secondary endpoints in this study was Question 3 of the Sexual Encounter Profile diary (SEP3). Timing of sexual activity was not restricted relative to when patients took CIALIS.

The efficacy results for patients with both ED and BPH, who received either CIALIS 5 mg for once daily use or placebo (N=408) are shown in Tables 21 and 22 and Figure 8.

CIALIS 5 mg for once daily use resulted in statistically significant improvements in the total IPSS and in the EF domain of the IIEF questionnaire. CIALIS 5 mg for once daily use also resulted in statistically significant improvement in SEP3. CIALIS 2.5 mg did not result in statistically significant improvement in the total IPSS.

Table 21: Mean IPSS and IIEF EF Domain Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo	CIALIS 5 mg	p-value
Total Symptom Score (IPSS)			
	(N=193)	**(N=206)**	
Baseline	18.2	18.5	
Change from Baseline to Week 12	-3.8	-6.1	<.001
EF Domain Score (IIEF EF)			
	(N=188)	**(N=202)**	
Baseline	15.6	16.5	
Endpoint	17.6	22.9	
Change from Baseline to Week 12	1.9	6.5	<.001

Table 22: Mean SEP Question 3 Changes in the CIALIS 5 mg for Once Daily Use Study in Patients with ED and BPH

	Placebo (N=187)	CIALIS 5 mg (N=199)	p-value
Maintenance of Erection (SEP3)			
Baseline	36%	43%	
Endpoint	48%	72%	
Change from Baseline to Week 12	12%	32%	<.001

CIALIS for once daily use resulted in improvement in the IPSS total score at the first scheduled observation (week 2) and throughout the 12 weeks of treatment (*see* Figure 8).

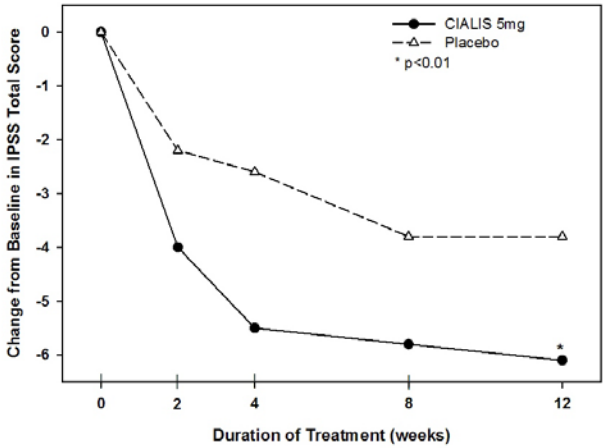


Figure 8: Mean IPSS Changes in ED/BPH Patients by Visit in Study L

In this study, the effect of CIALIS 5 mg once daily on Q_{max} was evaluated as a safety endpoint. Mean Q_{max} increased from baseline in both the treatment and placebo groups (CIALIS 5 mg: 1.6 mL/sec, placebo: 1.2 mL/sec); however, these changes were not significantly different between groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

CIALIS (tadalafil) is supplied as follows:

Four strengths of almond-shaped tablets are available in different sizes and different shades of yellow, and supplied in the following package sizes:

2.5 mg tablets debossed with “C 2 1/2”
Blisters of 2 x 15 NDC 0002-4465-34
5 mg tablets debossed with “C 5”
Bottles of 30 NDC 0002-4462-30
Blisters of 2 x 15 NDC 0002-4462-34
10 mg tablets debossed with “C 10”
Bottles of 30 NDC 0002-4463-30
20 mg tablets debossed with “C 20”
Bottles of 30 NDC 0002-4464-30

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

“See FDA-approved patient labeling (Patient Information)”

17.1 Nitrates

Physicians should discuss with patients the contraindication of CIALIS with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of CIALIS with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of CIALIS. In such a patient, who has taken 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 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 CIALIS should seek immediate medical attention *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

17.2 Cardiovascular Considerations

Physicians should consider the potential cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Physicians should advise patients who experience symptoms upon initiation of sexual activity to refrain from further sexual activity and seek immediate medical attention *[see Warnings and Precautions (5.1)]*.

17.3 Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should discuss with patients the potential for CIALIS to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.4 Potential for Drug Interactions When Taking CIALIS for Once Daily Use

Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing CIALIS for once daily use, especially the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives and potent inhibitors of cytochrome P450 3A4) and with substantial consumption of alcohol. *[see Dosage and Administration (2.7), Warnings and Precautions (5.6), Drug Interactions (7.1, 7.2), Clinical Pharmacology (12.2), and Clinical Studies (14.2)]*.

17.5 Priapism

There have been rare reports of prolonged erections greater than 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. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.

17.6 Sudden Loss of Vision

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. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including possible 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. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a “crowded” optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including CIALIS, for this uncommon condition *[see Warnings and Precautions (5.4) and Adverse Reactions (6.2)]*.

17.7 Sudden Hearing Loss

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 Reactions (6.1, 6.2)]*.

17.8 Alcohol

Patients should be made aware that both alcohol and 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 CIALIS can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Warnings and Precautions (5.9), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.9 Sexually Transmitted Disease

The use of CIALIS offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

17.10 Recommended Administration

Physicians should instruct patients on the appropriate administration of CIALIS to allow optimal use.

For CIALIS for use as needed in men with ED, patients should be instructed to take one tablet at least 30 minutes before anticipated sexual activity. In most patients, the ability to have sexual intercourse is improved for up to 36 hours.

For CIALIS for once daily use in men with ED or ED/BPH, patients should be instructed to take one tablet at approximately the same time every day without regard for the timing of sexual activity. Cialis is effective at improving erectile function over the course of therapy.

For CIALIS for once daily use in men with BPH, patients should be instructed to take one tablet at approximately the same time every day.

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