34 mm

34 mm

34 mm

Tadalafil Tablets USP

13014
205016

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TADALAFIL TABLETS safely and effectively. See full prescribing information for TADALAFIL TABLETS.
TADALAFIL tablets, for oral use
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Warnings and Precautions (5.4) 05/2017

INDICATIONS AND USAGE

Tadalafil tablet 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 tadalafil tablets are used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks (1.4).

DOSAGE AND ADMINISTRATION

- *Tadalafil tablets 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).
- *Tadalafil tablets 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).
  Tadalafil tablets 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 tadalafil tablets to patients using any form of organic nitrate is contraindicated. Tadalafil tablets were shown to potentiate the hypotensive effect of nitrates (4.1).
- History of known serious hypersensitivity reaction to tadalafil tablets or ADCIRCA® (4.2)
- Administration with guanylate cyclase (GC) stimulators, such as, riociguat (4.3)

WARNINGS AND PRECAUTIONS

- Patients should not use tadalafil tablets if sex is inadvisable due to cardiovascular status (5.1).
- Use of tadalafil tablets with alpha-blockers, antihypertensives or substantial amounts of alcohol (>5 units) may lead to hypotension (5.6, 5.9).
- Tadalafil tablets are 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 tadalafil tablets are 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 tadalafil tablets with caution in patients predisposed to priapism (5.3).
- Patients should stop tadalafil tablets 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). Tadalafil tablets 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 tadalafil tablets and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5).
- Prior to initiating treatment with tadalafil tablets 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 www.umedicalabs.com at 1-855-288-577 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Tadalafil tablets can potentiate the hypotensive effects of nitrates, alpha-blockers, antihypertensives or alcohol (7.1).
- CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase tadalafil tablets exposure (2.7, 5.10, 7.2) requiring dose adjustment:
  - Tadalafil tablets can be used as needed: no more than 10 mg every 72 hours
  - Tadalafil tablets for once daily use: dose not to exceed 2.5 mg
- CYP3A4 inducers (e.g. rifampin) decrease tadalafil tablets 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: 12/2023

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Erectile Dysfunction

Tadalafil tablets are indicated for the treatment of erectile dysfunction (ED).

1.2 Benign Prostatic Hyperplasia

Tadalafil tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

1.3 Erectile Dysfunction and Benign Prostatic Hyperplasia

Tadalafil tablets are indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

1.4 Limitation of Use

If tadalafil tablets are used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil tablets beyond 26 weeks in combination with finasteride is not recommended for benefit of tadalafil tablets beyond 26 weeks in unknown *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

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

2.1 Tadalafil tablets for Use as Needed for Erectile Dysfunction

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

2.2 Tadalafil tablets for Once Daily Use for Erectile Dysfunction

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

2.3 Tadalafil tablets for Once Daily Use for Benign Prostatic Hyperplasia

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

2.4 Tadalafil tablets for Once Daily Use for Erectile Dysfunction and Benign Prostatic Hyperplasia

The recommended dose of tadalafil tablets 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

Tadalafil tablets may be taken without regard to food.

2.6 Use in Specific Populations

Renal Impairment

Tadalafil tablets for Use as Needed

- Creatinine clearance 30 to 50 mL/min: A starting dose of 5 mg for use as needed in most patients is 10 mg, taken prior to anticipated sexual activity.
- Creatinine clearance less than 30 mL/min or on hemodialysis: A starting dose of 5 mg not more than once in every 72 hours. *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.7)]*.

Tadalafil tablets for Once Daily Use

Erectile Dysfunction

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

Hepatic Impairment

Tadalafil tablets for Use as Needed

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

Tadalafil tablets for Once Daily Use

- Mild or moderate (Child Pugh Class A or B): Tadalafil tablets for once daily use has not been extensively evaluated in patients with hepatic impairment and therefore, caution is advised. Severe (Child Pugh Class C): Tadalafil tablets for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of tadalafil tablets 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 tadalafil tablets are 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 tablets should be initiated at the lowest recommended dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

BPH — Tadalafil tablets are 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

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

Tadalafil tablets for Once Daily Use — For patients taking concomitant 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 yellow color.
2.5 mg tablets debossed with "TA0"
5 mg tablets debossed with "T10"
10 mg tablets debossed with "T20"
20 mg tablets debossed with "T30"

4 CONTRAINDICATIONS

4.1 Nitrates

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

4.2 Hypersensitivity Reactions

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

4.3 Concomitant Guanylate Cyclase (GC) Stimulators

Do not use tadalafil tablets in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including tadalafil tablets may potentiate the hypotensive effects of GC stimulators.

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 tadalafil tablets, 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 tadalafil tablets, 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 tablets. In such a patient, who has taken tadalafil tablets, 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 tablets 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 tablets 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 tadalafil tablets, and therefore until further information is available, tadalafil tablets are 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 tadalafil tablets, 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 Tadalafil tablets for Once Daily Use

Physicians should be aware that tadalafil tablets for once daily use provide continuous plasma tadalafil levels and should consider this when evaluating the potential for interactions with medications (e.g., nitrates, alpha-blockers, antihypertensives 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.

Tadalafil tablets 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 tadalafil tablets, 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 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 the preceding 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 comparable risk estimate of 2.27 (95% CI 0.98, 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 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 tadalafil tablets, should be used with caution in such 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 those without crowded optic discs, however there is insufficient support screening of prospective users of PDE5 inhibitors, including tadalafil tablets, 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 tadalafil tablets, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which have been reported in temporal association by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including tadalafil tablets. 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)]*.

Patients with pre-existing hearing impairment should be considered.

5.6 Alpha-blockers and Antihypertensives

Administration of tadalafil tablets to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, tadalafil tablets were shown to potentiate the hypotensive effect of nitrates *[see Contraindications (4.1)]*.

Administration of tadalafil tablets to patients using alpha-blockers may lead to hypotension in some patients who are susceptible to vasodilators, including PDE5 inhibitors. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Administration of vasodilators, including PDE5 inhibitors, to patients taking alpha-blockers may produce a further lowering of blood pressure in some patients who are susceptible to this interaction. These effects are most likely to occur within a few days of initiating therapy with a new vasodilator, or with an increase in dosage of a vasodilator. In such patients, it is prudent to initiate tadalafil tablets at the lowest dose. 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 tadalafil tablets, for this uncommon condition *[see Warnings and Precautions (5.4) and Adverse Reactions (6.2)]*.

5.7 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including tadalafil tablets, 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 tablets. 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)]*.

5.8 Alcohol

Patients should be made aware that both alcohol and tadalafil tablets, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be expected. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with tadalafil tablets 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)]*.

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

Tadalafil tablets are metabolized predominantly by CYP3A4 in the liver. The dose of tadalafil tablets for use as needed should not exceed 10 mg in 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 taking tadalafil tablets 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 tadalafil tablets and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take tadalafil tablets 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. Tadalafil tablets 20 mg did not have an appreciable effect on platelet aggregation induced by platelet-active agents, ulceration. Although tadalafil tablets have 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 tadalafil tablets 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 tadalafil 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 used to predict the rate of adverse reactions to the use 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 tablets 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 tadalafil tablets for use as needed, over 1300 and 1000 subjects were treated for at least 6 months and 1 year, respectively.

Tadalafil tablets 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 tadalafil tablets treated subjects was 3.4% (n=1,053), compared to 1.4% in placebo treated patients.

When taken as needed in these placebo-controlled clinical trials, the following adverse reactions were reported (see Table 1) for tadalafil tablets for use as needed:

Table 1: Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with tadalafil tablets (10 or 20 mg) and Not Reported at a Higher Frequency in Drug Than Placebo in the Eight Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for tadalafil tablets for Use as Needed for ED

Adverse Reaction	Placebo (N=579)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=354)	Tadalafil 20 mg (N=435)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	2%	3%	4%
Nasal congestion	1%	2%	3%	3%
Flushing†	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

† The term flushing includes: facial flushing and flushing

Tadalafil tablets for Once Daily Use for ED

In three placebo-controlled clinical trials of 12 to 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 Tadalafil Tablets 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 tadalafil tablets for Once Daily Use for ED

Adverse Reaction	Placebo (N=248)	Tadalafil 2.5 mg (N=258)	Tadalafil 5 mg (N=186)
Headache	5%	3%	6%
Dyspepsia	2%	4%	5%
Myalgia	4%	4%	3%
Back pain	1%	3%	3%
Upper respiratory tract infection	1%	3%	3%
Flushing	1%	3%	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 Tadalafil tablets for Once Daily Use (2.5 or 5 mg) and Not Reported at a Higher Frequency in Drug than Placebo in the Placebo-Controlled Study of 24 Weeks Treatment Duration for tadalafil tablets for Once Daily Use for ED

Adverse Reaction	Placebo (N=268)	Tadalafil 2.5 mg (N=87)	Tadalafil 5 mg (N=87)
Nasopharyngitis	5%	6%	6%
Gastroenteritis	2%	3%	5%
Back pain	3%	5%	2%
Upper respiratory tract infection	0%	3%	4%
Diarrhea	1%	2%	4%
Gastroesophageal reflux disease	0%	3%	2%
Myalgia	2%	4%	2%
Hypertension	0%	1%	3%
Nasal congestion	0%	0%	4%

Tadalafil tablets for Once Daily Use for BPH and for ED and BPH

In three placebo-controlled clinical trials of 12 weeks duration, for men 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 tadalafil tablets treated subjects was 2.1% (n=1,176) in placebo-treated patients. The following adverse reactions were reported to discontinuation reported by at least 2 patients treated 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 Tadalafil tablets for Once Daily Use (5 mg) and More Frequent on Drug than Placebo in These Placebo-Controlled Studies of 12 Weeks Treatment Duration, Including Two Studies for Tadalafil tablets for Once Daily Use for BPH and One Study for ED and BPH

Adverse Reaction	Placebo (N=576)	Tadalafil 5 mg (N=501)
Headache	2.3%	4.1%
Dyspepsia	0.2%	2.4%
Back pain	1.4%	2.2%
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 tadalafil tablets 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 administration 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 tadalafil tablets 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 an underlying pathology. Incidence rates for tadalafil tablets for once daily use for ED, BPH and BPH/ED are described in Tables 2, 3 and 4. In studies of tadalafil tablets 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 placebo-controlled studies with tadalafil tablets for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with tadalafil tablets (2.5% of patients) *[see Use in Specific Populations (8.5)]*.

Across all studies with any tadalafil tablets 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 tablets for once daily use or use as needed. A causal relationship of these events to tadalafil tablets is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use, and those events reported in the placebo group.

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, dyspepsia, esophagitis, gastritis, GGTP increased, loose stools, nausea, upper abdominal pain, vomiting, gastroesophageal reflux disease, hemorrhoidal hemorrhage, rectal hemorrhage

Musculoskeletal — arthralgia, neck pain

Nervous — dizziness, hyperthesia, insomnia, paresthesia, sormolence, vertigo

Renal and Urinary — renal pain

Respiratory — dyspnea, epistaxis, pharyngitis

Skin and Appendage — 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 tadalafil tablets. Because they 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, frequency of reporting, lack of clear alternative explanations, 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 tablets. 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 tadalafil tablets without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil tablets and sexual activity. It is not possible to determine whether these events are related to tadalafil tablets, to sexual activity, to the underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

Eye or a Whole — hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis

Nervous — migraine, seizure and seizure recurrence, transient global amnesia

Ophthalmologic — vision loss due to nonarteritic anterior ischemic optic neuropathy, retinal vein occlusion

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported in temporal association with the intake of products with the use of PDE5 inhibitors, including tadalafil tablets. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION. Unilateral vision loss has been reported for tadalafil tablets for once daily for ED, reviewed for up to 2 years, for 50-, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking *[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 tadalafil tablets. In some of the cases, medical conditions and other factors are reported that may be a cause for sudden decrease or loss of hearing, however in many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related to the use of tadalafil tablets, to the underlying risk factors for hearing loss, to 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 Tadalafil tablets

Nitrates — Administration of tadalafil tablets to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology stud