TADAFIL
2.5 mg/5 mg/10 mg/20 mg
Film-Coated Tablet
Phosphodiesterase Type-5 Inhibitor
2068489

TADALAFIL

TADAFIL 2.5
TADAFIL 5
TADAFIL 10
TADAFIL-20
2.5 mg/5 mg/10 mg/20 mg
Film-Coated Tablet
Phosphodiesterase Type-5 Inhibitor

FORMULATION
Tadalafil Tablets 2.5 mg:
Each film-coated tablet contains:
Tadalafil, USP..... 2.5 mg

Tadalafil Tablets 5 mg:
Each film-coated tablet contains:
Tadalafil, USP..... 5 mg

Tadalafil Tablets 10 mg:
Each film-coated tablet contains:
Tadalafil, USP..... 10 mg

Tadalafil Tablets 20 mg:
Each film-coated tablet contains:
Tadalafil, USP..... 20 mg

PRODUCT DESCRIPTION
Tadalafil Tablets USP 2.5 mg:
Blue colour, round shaped, biconvex, film coated tablets debossed with 'T18' on one side and 'H' on the other side.

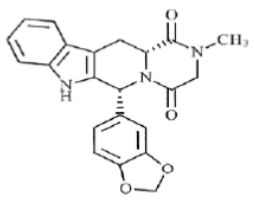
Tadalafil Tablets USP 5 mg:
White colour, round shaped, biconvex, film coated tablets debossed with 'T17' on one side and 'H' on the other side.

Tadalafil Tablets USP 10 mg:
White colour, capsule shaped, biconvex, film coated tablets debossed with 'T16' on one side and 'H' on the other side.

Tadalafil Tablets USP 20 mg:
White colour, capsule shaped, biconvex, film coated tablets debossed with 'T15' on one side and 'H' on the other side.

Tadalafil is (6*R*-12a*R*)-6-(1,3-Benzodioxol-5-yl)-2-methyl- 2, 3, 6, 7, 12, 12a-hexahydro-2-methylpyrazino[1',2': 1,6]pyrido[3,4-*b*]indole-1,4-dione.

The molecular formula is C22H19N3O4 and the molecular weight is 389.41. The chemical structure of Tadalafil is:



Tadalafil is white or almost white crystalline powder. Sample was slightly hygroscopic. Freely Soluble in dimethyl sulfoxide, dimethylformamide, slightly soluble in methylene chloride and practically insoluble in water.

Tadalafil contain the following inactive ingredients: Lactose Monohydrate, Copovidone, Colloidal Silicon Dioxide, (Aerosil 200), Polyoxyl 40 hydrogenated castor oil (Kolliphor RH 40), Lactose Monohydrate, (Super Tab 11 SD), Micro crystalline cellulose, (Avicel PH 1 02), Croscarmellose sodium (Ac-disol), Colloidal Silicon Dioxide, (Aerosil 200), Magnesium stearate (Ligarned MF-2-V), Opadry II White 32K580001, Purified water

THERAPEUTIC INDICATIONS
Erectile Dysfunction
Tadalafil is indicated for the treatment of erectile dysfunction (ED).

Benign Prostatic Hyperplasia
TADALAFIL is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Erectile Dysfunction And Benign Prostatic Hyperplasia
TADALAFIL is indicated for the treatment of ED and the signs and symptoms of BPH (ED/BPH).

Limitation Of Use
If TADALAFIL is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of TADALAFIL decreases from 4 weeks until 26 weeks, and the incremental benefit of TADALAFIL beyond 26 weeks is unknown

POSOLOGY AND METHOD OF ADMINISTRATION

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

TADALAFIL For Use As Needed For Erectile Dysfunction
- The recommended starting dose of TADALAFIL 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 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, this should be taken into consideration.

TADALAFIL For Once Daily Use For Erectile Dysfunction
- The recommended starting dose of TADALAFIL 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 dose for once daily use may be increased to 5 mg, based on individual efficacy and tolerability.

TADALAFIL For Once Daily Use For Benign Prostatic Hyperplasia
- The recommended dose of TADALAFIL for once daily use is 5 mg, taken at approximately the same time every day.
- When therapy for BPH is initiated with TADALAFIL and finasteride, the recommended dose of TADALAFIL for once daily use is 5 mg, taken at approximately the same time every day for up to 26 weeks.

TADALAFIL For Once Daily Use For Erectile Dysfunction And Benign Prostatic Hyperplasia
The recommended dose of TADALAFIL for once daily use is 5 mg, taken at approximately the same time every day, without regard to timing of sexual activity.

Use With Food
TADALAFIL may be taken without regard to food.

Use In Specific Populations
Renal Impairment
TADALAFIL 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** and **Use In Specific Populations**].

TADALAFIL For Once Daily Use
Erectile Dysfunction
- Creatinine clearance less than 30 mL/min or on hemodialysis: TADALAFIL for once daily use is not recommended [see **WARNINGS AND PRECAUTIONS** and **Use In Specific Populations**].

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 for once daily use is not recommended [see **WARNINGS AND PRECAUTIONS** and **Use In Specific Populations**].

Hepatic Impairment
TADALAFIL 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 TADALAFIL 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 is not recommended [see **WARNINGS AND PRECAUTIONS** and **Use In Specific Populations**].

TADALAFIL For Once Daily Use
- Mild or moderate (Child Pugh Class A or B): TADALAFIL for once daily use has not been extensively evaluated in patients with hepatic impairment. Therefore, caution is advised if TADALAFIL for once daily use is prescribed to these patients.
- Severe (Child Pugh Class C): The use of TADALAFIL is not recommended [see **WARNINGS AND PRECAUTIONS** and **Use In Specific Populations**].

Concomitant Medications
Nitrates
Concomitant use of nitrates in any form is contraindicated [see **CONTRAINDICATIONS**].

Alpha-Blockers
ED — When TADALAFIL is coadministered with an alpha-blocker in patients being treated for ED, patients should be stable on alpha-blocker therapy prior to initiating treatment, and TADALAFIL should be initiated at the lowest recommended dose [see **WARNINGS AND PRECAUTIONS**, **DRUG INTERACTIONS**, and **CLINICAL PHARMACOLOGY**].

BPH — TADALAFIL is not recommended for use in combination with alpha-blockers for the treatment of BPH [see **WARNINGS AND PRECAUTIONS**, **DRUG INTERACTIONS**, and **CLINICAL PHARMACOLOGY**].

CYP3A4 Inhibitors
TADALAFIL for Use as Needed — For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the maximum recommended dose of TADALAFIL is 10 mg, not to exceed once every 72 hours [see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**].

TADALAFIL 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** and **DRUG INTERACTIONS**].

CONTRAINDICATIONS
Nitrates
Administration of TADALAFIL to patients who are using any form of organic nitrate, either regularly and/or intermittently, is contraindicated. In clinical pharmacology studies, TADALAFIL was shown to potentiate the hypotensive effect of nitrates [see **CLINICAL PHARMACOLOGY**].

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

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

DRUG INTERACTIONS
Potential For Pharmacodynamic Interactions With TADALAFIL
Nitrates
Administration of TADALAFIL to patients who are using any form of organic nitrate, is contraindicated. In clinical pharmacology studies, TADALAFIL was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken TADALAFIL, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of TADALAFIL 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**, **CONTRAINDICATIONS**, and **CLINICAL PHARMACOLOGY**].

Alpha-Blockers
Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including TADALAFIL, 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**, **WARNINGS AND PRECAUTIONS**, and **CLINICAL PHARMACOLOGY**].

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** and **CLINICAL PHARMACOLOGY**].

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 TADALAFIL 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** and **CLINICAL PHARMACOLOGY**].

Potential For Other Drugs To Affect TADALAFIL
[See **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**].

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.

H2 Antagonists (e.g. Nizatidine)
An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics.

Cytochrome P450 Inhibitors
TADALAFIL 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 Cmax 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 Cmax by 15%, relative to the values for tadalafil 10 mg alone [see **DOSAGE AND ADMINISTRATION**].

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

HIV Protease Inhibitor
Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in Cmax, 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 Cmax, 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**].

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 Cmax by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of TADALAFIL for once daily use; the magnitude of decreased efficacy is unknown.

Potential For TADALAFIL To Affect Other Drugs
Aspirin
Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Cytochrome P450 Substrates
TADALAFIL 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.

WARNINGS AND PRECAUTIONS
WARNINGS
Included as part of the **PRECAUTIONS** section.

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, it is important to note the following:

Cardiovascular
Physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Therefore, treatments for erectile dysfunction, including TADALAFIL, 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. In such a patient, who has taken TADALAFIL, 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 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 should seek immediate medical attention. [see **CONTRAINDICATIONS** and **PATIENT INFORMATION**].

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, and therefore until further information is available, TADALAFIL 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**]. While this effect should not be of consequence in most patients, prior to prescribing TADALAFIL, 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.

Potential For Drug Interactions When Taking TADALAFIL For Once Daily Use
Physicians should be aware that TADALAFIL 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**].

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

Effects On The Eye
Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including TADALAFIL, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision, including permanent loss of vision, that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50.

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

Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION [see **ADVERSE REACTIONS**].

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, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including TADALAFIL, for this uncommon condition.

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

Sudden Hearing Loss
Physicians should advise patients to stop taking PDE5 inhibitors, including TADALAFIL, 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. 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**].

Alpha-blockers And Antihypertensives
Physicians should discuss with patients the potential for TADALAFIL to augment the blood-pressure-lowering effect of alpha-blockers and antihypertensive medications [see **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY**].

Caution is advised when PDE5 inhibitors are coadministered with alpha-blockers. PDE5 inhibitors, including TADALAFIL, 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** and **CLINICAL PHARMACOLOGY**], 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** and **DRUG INTERACTIONS**].

BPH
- The efficacy of the coadministration of an alpha-blocker and TADALAFIL 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 TADALAFIL and alpha-blockers is not recommended for the treatment of BPH. [see **DOSAGE AND ADMINISTRATION**, **DRUG INTERACTIONS**, and **CLINICAL PHARMACOLOGY**].
- Patients on alpha-blocker therapy for BPH should discontinue their alpha-blocker at least one day prior to starting TADALAFIL for once daily use for the treatment of BPH.

Renal Impairment
TADALAFIL For Use As Needed
TADALAFIL should be limited to 5 mg not more than once in every 72 hours in patients with creatinine clearance less than 30 mL/min or end-stage renal disease on hemodialysis. The starting dose of TADALAFIL 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**].

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

BPH And ED/BPH
Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis, TADALAFIL 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**, **Use In Specific Populations**, and **CLINICAL PHARMACOLOGY**].

Hepatic Impairment
TADALAFIL For Use As Needed
In patients with mild or moderate hepatic impairment, the dose of TADALAFIL should not exceed 10 mg. Because of insufficient information in patients with severe hepatic impairment, use of TADALAFIL in this group is not recommended [see **Use In Specific Populations**].

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

Alcohol
Patients should be made aware that 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. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with TADALAFIL 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**].

Concomitant Use Of Potent Inhibitors Of Cytochrome P450 3A4 (CYP3A4)
TADALAFIL is metabolized predominantly by CYP3A4 in the liver. The dose of TADALAFIL 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**]. In patients taking potent inhibitors of CYP3A4 and TADALAFIL for once daily use, the maximum recommended dose is 2.5 mg [see **DOSAGE AND ADMINISTRATION**].

Combination With Other PDE5 Inhibitors Or Erectile Dysfunction Therapies
The safety and efficacy of combinations of TADALAFIL and other PDE5 inhibitors or treatments for erectile dysfunction have not been studied. Inform patients not to take TADALAFIL with other PDE5 inhibitors, including ADCIRCA.

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 has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although TADALAFIL has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment and caution.

Counseling Patients About Sexually Transmitted Diseases
The use of TADALAFIL 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.

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.

Nitrates
Physicians should discuss with patients the contraindication of TADALAFIL with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of TADALAFIL 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 TADALAFIL. In such a patient, who has taken TADALAFIL, 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 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 should seek immediate medical attention [see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**].

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colour: 1(Black)

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Guanylate Cyclase (GC) Stimulators
Physicians should discuss with patients the contraindication of TADALAFIL with any use of a GC stimulator, such as riociguat, for pulmonary arterial hypertension. Patients should be counseled that the concomitant use of TADALAFIL with GC stimulators may cause blood pressure to drop to an unsafe level.

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**].

Concomitant Use With Drugs Which Lower Blood Pressure
Physicians should discuss with patients the potential for TADALAFIL to augment the blood-pressure-lowering effect of alpha-blockers, and antihypertensive medications [see **WARNINGS AND PRECAUTIONS**, **DRUG INTERACTIONS**, and **CLINICAL PHARMACOLOGY**].

Potential For Drug Interactions When Taking TADALAFIL For Once Daily Use
Physicians should discuss with patients the clinical implications of continuous exposure to tadalafil when prescribing TADALAFIL 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**, **WARNINGS AND PRECAUTIONS**, **DRUG INTERACTIONS**, **CLINICAL PHARMACOLOGY**, and **Clinical Studies**].

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.

Sudden Loss Of Vision
Physicians should advise patients to stop use of all PDE5 inhibitors, including TADALAFIL, 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. 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 TADALAFIL, for this uncommon condition [see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**].

Sudden Hearing Loss
Physicians should advise patients to stop taking PDE5 inhibitors, including TADALAFIL, 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. 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**].

Alcohol
Patients should be made aware that 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. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., 5 units or greater) in combination with TADALAFIL 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**, **DRUG INTERACTIONS**, and **CLINICAL PHARMACOLOGY**].

Sexually Transmitted Disease
The use of TADALAFIL 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.

Recommended Administration
Physicians should instruct patients on the appropriate administration of TADALAFIL to allow optimal use.

For TADALAFIL 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 TADALAFIL 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. Tadalafil is effective at improving erectile function over the course of therapy.

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

Use In Specific Populations
Pregnancy
Risk Summary
TADALAFIL is not indicated for use in females.

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

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

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

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

Lactation
Risk Summary
TADALAFIL is not indicated for use in females.

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

Females And Males Of Reproductive Potential
Infertility
Based on the data from 3 studies in adult males, tadalafil decreased sperm concentrations in the study of 10 mg tadalafil for 6 months and the study of 20 mg tadalafil for 9 months. This effect was not seen in the study of 20 mg tadalafil taken for 6 months. There was no adverse effect of tadalafil 10 mg or 20 mg on mean concentrations of testosterone, luteinizing hormone or follicle stimulating hormone. The clinical significance of the decreased sperm concentrations in the two studies is unknown. There have been no studies evaluating the effect of tadalafil on fertility in men [see **CLINICAL PHARMACOLOGY**].
Based on studies in animals, a decrease in spermatogenesis was observed in dogs, but not in rats [see **Nonclinical Toxicology**].

Pediatric Use
TADALAFIL is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.

A randomized, double-blind, placebo-controlled trial in pediatric patients (7 to 14 years of age) with Duchenne muscular dystrophy, who received TADALAFIL 0.3 mg/kg, TADALAFIL 0.6 mg/kg, or placebo daily for 48 weeks failed to demonstrate any benefit of treatment with TADALAFIL on a range of assessments of muscle strength and performance.

Geriatric Use
Of the total number of subjects in ED clinical studies of tadalafil, approximately 19 percent were 65 and over, while approximately 2 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). However, in placebo-controlled studies with TADALAFIL for use as needed for ED, diarrhea was reported more frequently in patients 65 years of age and older who were treated with TADALAFIL (2.5% of patients) [see **ADVERSE REACTIONS**]. 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**].

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** and **WARNINGS AND PRECAUTIONS**].

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 Cmax 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** and **WARNINGS AND PRECAUTIONS**].

PHARMACOLOGICAL PROPERTIES
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.

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 TADALAFIL in patients taking any form of nitrates is contraindicated [see **CONTRAINDICATIONS**].

A study was conducted to assess the degree of interaction between nitroglycerin and tadalafil, should nitroglycerin be required in an emergency situation after tadalafil was taken. This was a double-blind, placebo-controlled, crossover study in 150 male subjects at least 40 years of age (including subjects with diabetes mellitus and/or controlled hypertension) and receiving daily doses of tadalafil 20 mg or matching placebo for 7 days. Subjects were administered a single dose of 0.4 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.

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

Effect On Blood Pressure When Administered With Alpha-Blockers
Six randomized, double-blinded, crossover clinical pharmacology studies were conducted to investigate the potential interaction of tadalafil with alpha-blocker agents in healthy male subjects [see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**]. 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.

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.

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

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

Alfuzosin
A single oral dose of tadalafil 20 mg or placebo was administered in a 2-period, crossover design to healthy subjects taking once-daily alfuzosin HCl 10 mg extended-release tablets, an alpha[1]-adrenergic blocker (N=17 completed subjects). Tadalafil or placebo was administered 4 hours after alfuzosin following a minimum of seven days of alfuzosin dosing.
Blood pressure was measured manually at 1, 2, 3, 4, 6, 8, 10, 20, and 24 hours after tadalafil or placebo dosing. There was 1 outlier (subject with a standing systolic blood pressure <85 mm Hg) following administration of tadalafil 20 mg. There were no subjects with a decrease from baseline in standing systolic blood pressure of >30 mm Hg at one or more time points. No severe adverse events potentially related to blood pressure effects were reported. No syncope was reported.

Effects On Blood Pressure When Administered With Antihypertensives
Amlodipine
A study was conducted to assess the interaction of amlodipine (5 mg daily) and tadalafil 10 mg. There was no effect of tadalafil on amlodipine blood levels and no effect of amlodipine on tadalafil blood levels. The mean reduction in supine systolic/diastolic blood pressure due to tadalafil 10 mg in subjects taking amlodipine was 3/2 mm Hg, compared to placebo. In a similar study using tadalafil 20 mg, there were no clinically significant differences between tadalafil and placebo in subjects taking amlodipine.

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

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

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

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

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

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

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

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

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

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

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

Absorption
After single oral-dose administration, the maximum observed plasma concentration (Cmax) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.

The rate and extent of absorption of tadalafil are not influenced by food; thus TADALAFIL may be taken with or without food.

Distribution
The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.

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

Metabolism
Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Excretion
The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Geriatric
Healthy male elderly subjects (65 years or over) had a lower oral clearance of tadalafil, resulting in 25% higher exposure (AUC) with no effect on Cmax relative to that observed in healthy subjects 19 to 45 years of age. No dose adjustment is warranted based on age alone. However, greater sensitivity to medications in some older individuals should be considered [see **Use In Specific Populations**].

Patients With Diabetes Mellitus
In male patients with diabetes mellitus after a 10 mg tadalafil dose, exposure (AUC) was reduced approximately 19% and Cmax was 5% lower than that observed in healthy subjects. No dose adjustment is warranted.

Patients With BPH
In patients with BPH following single and multiple-doses of 20 mg tadalafil, no statistically significant differences in exposure (AUC and Cmax) were observed between elderly (70 to 85 years) and younger (≤60 years of age) subjects. No dose adjustment is warranted.

OVERDOSE
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.

Availability
Clear PVC/PE/Aclar-Alu Blister Pack x 10's (Box of 30's)

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Please seek medical attention immediately at the first sign of any adverse drug reaction.

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