PRODUCT MONOGRAPH

Pr ADCIRCA®

(tadalafil tablets)

20 mg

cGMP-Specific Phosphodiesterase Type 5 Inhibitor

Treatment of Pulmonary Arterial Hypertension

3650 Danforth Avenue
Toronto, Ontario M1N 2E8

www.lilly.ca

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Table of Contents

PrADCIRCA®

(tadalafil)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 20 mg	Croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

INDICATIONS AND CLINICAL USE

ADCIRCA (tadalafil) is indicated for the treatment of idiopathic ("primary") pulmonary arterial hypertension (PAH) or PAH associated with connective tissue disease, congenital heart disease or anorexigen use in patients with WHO functional class II or III who have not responded to conventional therapy.

CONTRAINDICATIONS

- Administration of ADCIRCA to patients who are using any form of organic nitrate (e.g., oral, sublingual, transdermal, by inhalation), either regularly and/or intermittently, is contraindicated, due to the risk of developing potentially severe hypotension.
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- ADCIRCA is contraindicated in patients with previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see WARNINGS AND PRECAUTIONS).
- The co-administration of PDE5 inhibitors, including ADCIRCA®, with guanylate cyclase stimulators, such as riociguat, is contraindicated because it could lead to potentially life-threatening episodes of symptomatic hypotension or syncope.

WARNINGS AND PRECAUTIONS

Cardiovascular

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. In such a patient, who has taken ADCIRCA, where nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of ADCIRCA 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 ADCIRCA should seek immediate medical attention.

As with other PDE5 inhibitors, tadalafil has mild systemic vasodilatory properties that may result in transient decreases in blood pressure. While this effect should not be of consequence in most patients, prior to prescribing ADCIRCA, 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.

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.

Pulmonary Veno-Occlusive Disease: Administration to patients with pulmonary veno-occlusive disease is not recommended. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered.

The following groups of patients with cardiovascular disease were excluded in the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (< 90/50 mm Hg), or uncontrolled hypertension.

Ophthalmologic

Physicians should advise patients to seek immediate 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 permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. An increased risk of acute NAION has been suggested from analyses of observational data in men with erectile dysfunction (ED) within 1 to 4 days of episodic PDE5 inhibitor use. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors (see ADVERSE REACTIONS).

- There is evidence that patients at risk for NAION may have abnormal optic discs (e.g. crowded disc) prior to development of the condition. If physicians are concerned about the overall risk of NAION, they should consider discussing these concerns with an ophthalmologist.

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.

Otologic

Physicians should advise patients to seek immediate 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 ADCIRCA. 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, Post-Market Adverse Drug Reactions).

Reproduction/ Urogenital

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

Long-term human studies with subjects 45 years or older have shown that tadalafil therapy may decrease sperm concentration in some patients, but the clinical relevance of this to human fertility is unknown.

Special Populations

Pregnant Women: There are no adequate and well controlled studies of ADCIRCA use in pregnant women. Animal reproduction studies in rats and mice revealed no evidence of fetal harm.

Non-teratogenic effects — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 9 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis (see TOXICOLOGY).

Nursing Women: It is not known whether tadalafil or its metabolites are excreted into human breast milk. Since many drugs are excreted in human milk, caution should be used when ADCIRCA is administered to nursing women.

Pediatric Use: The pharmacokinetics, safety or effectiveness of ADCIRCA in pediatric patients has not been established.

Use in the Elderly (> 65 years of age): Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or over 75 years of age. No dose adjustment is warranted based on age alone. However, a greater sensitivity to medications in some older individuals should be considered.

Use in Patients with Hepatic Impairment:

- *In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B):* See DOSAGE AND ADMINISTRATION.
- *In patients with severe hepatic cirrhosis (Child-Pugh Class C):* Patients with severe hepatic cirrhosis have not been studied and therefore dosing of ADCIRCA is not recommended. See DOSAGE AND ADMINISTRATION.

Use in Patients with Renal Impairment:

- *In patients with mild to moderate renal insufficiency:* See DOSAGE AND ADMINISTRATION.
- *In patients with severe renal insufficiency:* The use of ADCIRCA is not recommended due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians should discuss with patients the contraindication of ADCIRCA with regular and/or intermittent use of organic nitrates.

Physicians should advise patients to seek immediate 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 permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors when used in the treatment of male ED. Should the vision loss be diagnosed as NAION, continued use of ADCIRCA is

contraindicated (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Ophthalmologic).

ADVERSE REACTIONS

Overview

ADCIRCA was administered to 402 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 266 patients were treated for at least 182 days, and 110 patients were treated for at least 360 days. Adverse events (AEs) were reported with greater incidence in subjects taking tadalafil 40 mg; however, the rate of discontinuation due to AEs other than events related to worsening of PAH was similar in the tadalafil treatment group (3.8%) and in placebo (4.9%).

Clinical Trial Adverse Drug Reactions

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

Table 1: Treatment Emergent Adverse Events Reported by ≥3% of Patients in ADCIRCA 40 mg group and More Frequent than Placebo

EVENT	Placebo (%) (N=82)	Tadalafil 40 mg (%) (N=79)
Headache	15	42
Myalgia	4	14
Nasopharyngitis	7	13
Flushing	2	13
Respiratory Tract Infection (Upper and Lower)	6	13
Pain in Extremity	2	11
Diarrhea	10	11
Nausea	6	11
Back Pain	6	10
Dyspepsia	2	10
Nasal Congestion (including sinus congestion)	1	9
Chest Pain	1	6
Dyspnea	4	6
Fatigue	4	6
Vomiting	1	6
Upper Respiratory Tract Infection	4	6
Bronchitis	0	5
Gastroesophageal Reflux Disease	4	5
Edema	1	5
Rash	3	5
Constipation	1	4
Hot Flush	2	4
Insomnia	2	4
Menorrhagia (including increased uterine bleeding[a]	0	4
Musculoskeletal Stiffness	0	4
Non-Cardiac Chest Pain	0	4
Urinary Tract Infection	0	4
Abdominal discomfort	0	3
Abdominal pain	2	3
Abdominal pain lower	1	3
Abdominal pain upper	1	3
Sinusitis	0	3
Muscle Spasms	2	3
Vision Blurred	1	3

[a] Clinical non-MedDRA term to include reports of abnormal/excessive menstrual bleeding conditions such as menorrhagia, metrorrhagia or menometrorrhagia.

In the placebo controlled study, one subject (receiving tadalafil 10 mg) reported changes in colour vision. In the long-term extension study, no patients reported changes in colour vision.

Less Common Clinical Trial Adverse Drug Reactions

The following section identifies additional, less frequent events reported in the controlled clinical trial of ADCIRCA occurring in at least two subjects in the 40 mg treatment group, and greater than placebo. A causal relationship of these events to ADCIRCA is uncertain:

Blood and lymphatic disorders — Increased International Normalized Ratio

Body as a whole — chills, herpes zoster, onychomycosis, pain

Digestive — abdominal discomfort, abdominal pain (lower and upper), gastritis, stomach discomfort

Metabolic and nutrition disorders — hypercholesterolemia

Musculoskeletal — arthralgia, joint sprain, limb discomfort/pain

Nervous — hypesthesia, paresthesia

Psychiatric disorders — depression

Ophthalmologic — lacrimation increased, eyelid edema/swelling

Otologic — vertigo

Respiratory — lower respiratory tract infection, pharyngolaryngeal pain, rhinitis

Reproductive System — vaginal hemorrhage

Post-Market Adverse Drug Reactions

In postmarketing surveillance, adverse events that have been reported very rarely in temporal association in patients taking tadalafil include:

Body as a whole: hypersensitivity reactions including rash, urticaria, facial edema, Stevens-Johnson syndrome and exfoliative dermatitis.

Cardiovascular and cerebrovascular: Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia.

Hypotension (more commonly reported when tadalafil is given to patients who are already taking antihypertensive agents), hypertension and syncope.

Skin and subcutaneous tissues: hyperhidrosis (sweating).

Gastrointestinal: abdominal pain and gastroesophageal reflux.

Nervous system: migraine, transient global amnesia

Respiratory system: epistaxis (nose bleed)

Special senses: blurred vision, nonarteritic anterior ischemic optic neuropathy, retinal vein occlusion, visual field defect.

Otologic: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In many cases, medical follow-up information was limited.

Urogenital: priapism, prolonged erection.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIRCA

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

Alpha Blockers — Caution is advised when PDE5 inhibitors are coadministered with alpha blockers. PDE5 inhibitors, including ADCIRCA, 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, alfuzosin or tamsulosin (see ACTION AND CLINICAL PHARMACOLOGY).

Combination with Other PDE5 Inhibitors — Tadalafil is also marketed as CIALIS for treatment of male erectile dysfunction. The safety and efficacy of combinations of ADCIRCA with CIALIS or other PDE5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.

Antihypertensives — PDE5 inhibitors, including ADCIRCA, 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 ACTION AND CLINICAL PHARMACOLOGY).

Physicians should discuss with patients the potential for ADCIRCA to augment the blood pressure lowering effect of alpha blockers and antihypertensive medications (see ACTION AND CLINICAL PHARMACOLOGY).

In some patients, concomitant use of PDE5 inhibitors and alpha blockers can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating treatment with ADCIRCA. 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 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.

Alcohol — PDE5 inhibitors, including tadalafil, are vasodilators and may augment the blood-pressure-lowering effect of alcohol.

Tadalafil did not affect alcohol concentrations, and alcohol did not affect tadalafil concentrations. At high doses of alcohol (0.7 g/kg, mean maximum blood concentration 0.08%), the addition of tadalafil 10 or 20 mg did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When ADCIRCA was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone.

Potential for Other Drugs to Affect ADCIRCA

Cytochrome P450 Inducers — Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure. For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see DOSAGE AND ADMINISTRATION).

Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and C_{max} by 46%, relative to the values for tadalafil 10 mg alone.

Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced tadalafil (40 mg once per day) systemic exposure by 42% and C_{max} by 27% following multiple-dose co-administration.

Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure.

Cytochrome P450 Inhibitors — Tadalafil is metabolized predominantly by CYP3A4. In patients taking potent inhibitors of CYP3A4 such as ketoconazole, itraconazole or ritonavir, the use of ADCIRCA is not recommended (see DOSAGE AND ADMINISTRATION). Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure.

Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and C_{max} by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10 mg single-dose exposure (AUC) by 107% and C_{max} by 15%, relative to the values for tadalafil 10 mg alone (see DOSAGE AND ADMINISTRATION).

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

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

Antacids — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil (10 mg) 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 tadalafil (10 mg) pharmacokinetics.

Potential for ADCIRCA to Affect Other Drugs

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.

CYP1A2 (e.g. Theophylline) — Tadalafil (10 mg once per day) 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 (10 mg and 20 mg once per day) 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, Lovastatin or Bosentan) — Tadalafil (10 mg and 20 mg once per day) had no significant effect on exposure (AUC) to midazolam or lovastatin. Tadalafil (40 mg once per day) had no clinically significant effect on exposure (AUC and C_{max}) of bosentan, a substrate of CYP2C9 and CYP3A4, or its metabolites.

Aspirin — Tadalafil (10 mg and 20 mg once per day) did not potentiate the increase in bleeding time caused by aspirin.

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.

Combined Oral Contraceptives — At steady-state, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26% and C_{max} by 70% relative to oral contraceptive administered with placebo. There was no statistically significant effect of tadalafil on levonorgestrel.

Drug-Food Interactions

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of tadalafil.

Drug-Herb Interactions

Interaction with herbal products has not been established.

Drug-Laboratory Interactions

Interaction with laboratory tests has not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- ADCIRCA may be taken without regard to food.
- No dose adjustment is required in patients > 65 years of age.

Recommended Dose and Dosage Adjustment

The recommended dose of ADCIRCA is 40 mg taken once daily. Dividing the dose (40 mg) over the course of the day is not recommended.

Patients with Renal Insufficiency

- *Mild (creatinine clearance 51 to 80 mL/min) and Moderate (creatinine clearance 30 to 50 mL/min):* A starting dose of 20 mg once per day is recommended, the dose may be increased to 40 mg once per day based on individual efficacy and tolerability.
- *Severe (creatinine clearance < 30 mL/min):* The use of ADCIRCA is not recommended (see WARNINGS AND PRECAUTIONS).

Patients with Hepatic Impairment

- *Mild or moderate (Child Pugh Class A or B):* Due to limited clinical experience in patients with mild to moderate hepatic cirrhosis, a starting dose of 20 mg once per day is recommended. If ADCIRCA is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

- *Severe (Child Pugh Class C):* Patients with severe hepatic cirrhosis have not been studied and therefore dosing of ADCIRCA is not recommended (see WARNINGS AND PRECAUTIONS).

OVERDOSAGE

Single doses of up to 500 mg tadalafil have been given to healthy subjects, and multiple doses of 100 mg/day for 21 days have been given to patients with erectile dysfunction. Adverse events (e.g., headache, dyspepsia) were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension.

In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to elimination, as tadalafil is highly bound to plasma proteins.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

ADCIRCA (tadalafil), an oral treatment for pulmonary arterial hypertension, is a potent, selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Mechanism of Action

Tadalafil is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

In vitro Studies: See DETAILED PHARMACOLOGY

Pharmacodynamics

Effects on Blood Pressure and Heart Rate

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.

Nitrates — In clinical pharmacology studies, tadalafil (5 to 20 mg) was shown to potentiate the hypotensive effect of nitrates. Therefore, the use of ADCIRCA in patients taking any form of nitrates is contraindicated (see CONTRAINDICATIONS).

Antihypertensives —When tadalafil and certain oral antihypertensive medications (amlodipine, enalapril, metoprolol, bendrofluazide, angiotensin II receptor blockers) were assessed in drug interaction studies, tadalafil 10 or 20 mg doses did not result in clinically significant augmentation of the antihypertensive effects of those medications (see DRUG INTERACTIONS). Analysis of Phase 3 clinical trial data also showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medications.

Alpha-Blockers — The potential hemodynamic interactions of tadalafil with a non-selective alpha-blocker (doxazosin 4, 8 mg), a selective [1A] alpha-blocker (tamsulosin 0.4 mg) and a selective [1] alpha-blocker (alfuzosin 10 mg) were investigated in randomized, double-blind, crossover design studies. Blood pressure (BP) and heart rate were recorded before dosing and for 24 hours after dosing.

Tadalafil 20 mg augmented the hypotensive effect of 8 mg doxazosin by producing a mean maximal decrease in standing systolic BP (SBP) that was significantly greater than placebo (a mean difference of 9.8 mm Hg). Analysis of BP outliers showed that the number of subjects with a standing SBP of less than 85 mm Hg was greater after doxazosin plus tadalafil (28%) versus doxazosin plus placebo (6%). A further clinical pharmacology study was performed in order to investigate the lower dose of 4 mg doxazosin. The changes produced in that study were comparable to those observed in the earlier study. An additional study carried out with doxazosin (up to 4 mg daily) added to tadalafil (5 mg daily) also showed an augmentation of response, and symptoms associated with a decrease in blood pressure.

In subjects on tamsulosin, tadalafil 10 and 20 mg produced mean maximal decreases in standing SBP that were similar to placebo (mean difference of 1.7 and 2.3 mm Hg, respectively). No subject taking tamsulosin had a decrease in standing SBP less than 85 mm Hg. An additional study carried out with tamsulosin (0.4 mg) added to tadalafil (5 mg daily) also showed similar results with only two of the 37 subjects showing significantly low systolic and diastolic blood pressure following the administration of tadalafil and tamsulosin. In subjects receiving alfuzosin, tadalafil 20 mg also produced a maximal decrease in SBP that was not significantly different from that after placebo (mean difference of 4.35 mm Hg). One subject taking alfuzosin had an asymptomatic SBP of less than 85 mm Hg.

No vasodilatory adverse events were observed when tadalafil was administered with tamsulosin or alfuzosin. Dizziness, vertigo and syncope were reported following administration of tadalafil with doxazosin.

Effects on Other Cardiac/Hemodynamic Parameters

In patients with stable coronary artery disease (CAD) and demonstrable ischemia with exercise, tadalafil 10 mg was non-inferior to placebo with respect to effect on time to ischemia. In a separate double-blind, placebo-controlled study to evaluate the effects of ADCIRCA on myocardial perfusion in patients with CAD, tadalafil 20 mg had no significant effect on myocardial blood flow, both at rest and during pharmacological stress with dobutamine.

Tadalafil at doses up to 500 mg did not significantly change cardiac output and did not significantly impact patients' hemodynamic response to exercise.

No tadalafil-related changes in electrocardiographic measures, including QTc interval, were observed following administration of tadalafil single doses up to 500 mg and multiple doses of up to 100 mg once-daily for 21 days, to healthy subjects or patients with ED. ECGs were obtained pre- and post-dose, spanning the period from the expected T_{max} of tadalafil (2 hours) to the expected T_{max} of the primary metabolite (methylcatechol glucuronide, 24 hours).

The effect of a single 100-mg dose of tadalafil (2.5 times the recommended dose) 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). 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.

In clinical pharmacology studies, tadalafil 10 and 20 mg had no clinically significant effect on acetylsalicylic acid-induced prolongation of bleeding time or warfarin-induced changes in prothrombin time (See PRECAUTIONS, Drug Interactions).

Effects on Vision

In a study to assess the effects of a single dose of tadalafil 40 mg on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5 (*see* CLINICAL PHARMACOLOGY, Mechanism of Action). In addition, no effects were observed on visual acuity, electroretinograms, intraocular pressure, or pupillometry. Across all clinical studies with tadalafil 10 or 20 mg, reports of changes in colour vision were rare (< 0.1% of patients).

Effects on Sperm Characteristics

Three studies were conducted in men, ages 45-70 years, to assess the potential effect on spermatogenesis of tadalafil 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered once daily. In all 3 studies, there were no adverse effects on sperm morphology or sperm motility. There were also no significant changes in mean

concentrations of the reproductive hormones, testosterone, luteinizing hormone or follicle-stimulating hormone with either 10 or 20 mg of tadalafil compared to placebo. No decrease in sperm concentration was observed in the study of tadalafil 20 mg taken for 6 months. In the study of tadalafil 10 mg for 6 months and the study of tadalafil 20 mg for 9 months, results showed a statistically significant decrease in mean sperm concentration relative to placebo. The clinical relevance of this to human fertility is unknown. In the 9 month study (n=125 [tadalafil 20 mg], n=128 [placebo]), decreases in sperm concentration were in a few patients (but not all) associated with higher ejaculatory frequency, which may have resulted from tadalafil-related improvement in sexual function.

Exposure-Response Relationship

An analysis of tadalafil exposure and 6-minute walk distance in subjects with PAH in the Phase 3 Study, generated a model-predicted increase in 6-minute walk distance from baseline of 35.6 meters (30.5, 39.6 meters) and 38.09 meters (33.52, 43.20 meters) at 16 weeks of 20 mg and 40 mg daily administration, assuming the median (10th and 90th percentiles) steady-state tadalafil exposures.

Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 to 40 mg, an approximate 1.5-fold greater AUC is observed indicating a less than proportional increase in exposure over the entire dose range of 2.5 to 40 mg. During tadalafil 20- and 40-mg once-daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.3-fold than that after a single dose.

Absorption — Tadalafil is rapidly absorbed after oral administration and the maximum observed plasma concentration is achieved at a median time of 4 hours after dosing. The absolute bioavailability of tadalafil has not been determined.

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

Distribution — The mean apparent volume of distribution is approximately 77 L L at steady-state, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

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

Elimination — The mean oral clearance for tadalafil is 3.4 L/hr and the mean terminal half-life is 15 hours in healthy subjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Population pharmacokinetics — In patients with pulmonary hypertension not receiving concomitant bosentan, the average tadalafil exposure at steady-state following 40 mg was 26% higher when compared to those of healthy volunteers. There were no clinically relevant differences in C_{max} compared to healthy volunteers. The results suggest a lower clearance of tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

Special Populations and Conditions

Geriatric — The mean AUC value (4881 μg·h/L for 10 mg dose) in male subjects aged 65 to 78 years was approximately 25% higher than AUC (3896 μg·h/L) for subjects aged 19 to 45 years, while age had negligible effect on C_{max} values. This effect of age is not clinically significant and does not require a dose adjustment (See PRECAUTIONS, Use in the Elderly).

Children — Tadalafil has not been evaluated in individuals less than 18 years old.

Hepatic Insufficiency — In a clinical pharmacology study using tadalafil 10 mg, tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) was comparable to exposure in healthy subjects (see WARNINGS AND PRECAUTIONS, Use in Patients with Hepatic Impairment, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency — In clinical pharmacology studies using single-dose ADCIRCA 5 to 20 mg, tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal insufficiency, and in subjects with end-stage renal disease on dialysis. In dialysis patients, C_{max} was 41% higher than that observed in healthy subjects. Hemodialysis contributed negligibly to tadalafil elimination. (See WARNINGS AND PRECAUTIONS, Use in Patients with Renal Impairment, and DOSAGE AND ADMINISTRATION).

Patients with Diabetes — Tadalafil exposure (AUC 3454 μg·h/L for a 10 mg dose) in patients with diabetes was 19% lower, and the mean maximum plasma concentration (C_{max} of 184 μg/L) was 5% lower than that observed in healthy subjects. This difference in exposure does not require a dose adjustment.

Race — Pharmacokinetic studies have included subjects and patients from different ethnic groups, and no differences in the typical exposure to tadalafil have been identified. No dose adjustment is warranted.

Gender — In healthy female and male subjects following single and multiple-doses of tadalafil, no clinically relevant differences in exposure (AUC and Cmax) were observed. No dose adjustment is warranted.

STORAGE AND STABILITY

Store at controlled room temperature, 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ADCIRCA (tadalafil) is supplied as 20 mg orange, film-coated, almond-shaped tablets, debossed with "4467".

Each tablet contains 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

Availability:

- Blisters of 56 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

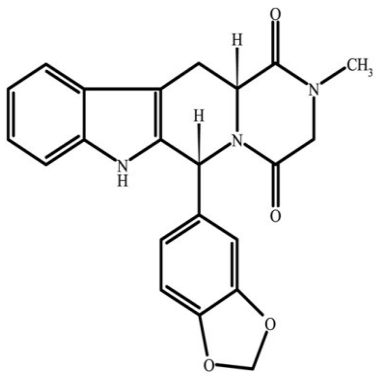
Common Name: Tadalafil

Chemical Name: pyrazino[1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)

Molecular Formula: $C_{22}H_{19}N_3O_4$

Molecular Weight: 389.41

Structural Formula:



Physicochemical Properties: It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol.

Melting Point: 303°C – 306°C

CLINICAL TRIALS

ADCIRCA for Pulmonary Arterial Hypertension

A randomized, double-blind, 16 week placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension (PAH, defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) ≥ 3 Wood units via right heart catheterization). Allowed background therapy included bosentan (maintenance dosing up to 125 mg twice daily) and chronic anticoagulation, whereas excluded therapy consisted of a prostacyclin or analogue, L-arginine, phosphodiesterase inhibitor, or other chronic PAH medication.

Subjects were randomly assigned to 1 of 5 treatment groups (tadalafil 2.5, 10, 20, 40 mg, or placebo) in a 1:1:1:1:1 ratio. Subjects were at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen disease, anorexigen use, human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt (for example, ventricular septal defect, patent ductus arteriosus). Patients with a history of left-sided heart disease, severe renal insufficiency or pulmonary hypertension related to conditions other than specified in the inclusion criteria were not eligible for enrollment.

The mean age of all subjects was 54 years (range 14 - 90 years) with the majority of subjects being Caucasian (80.5%) and female (78.3%). Pulmonary arterial hypertension (PAH) etiologies were predominantly idiopathic PAH (61.0%) and related to collagen vascular disease (23.5%). More than half (53.3%) of the subjects in the study were receiving concomitant bosentan therapy. The majority of subjects had a World Health Organization (WHO) Functional Class III (65.2%) or II (32.1%). The mean baseline 6-minute walk distance (6-MWD) was 343.6 meters. There were no major differences among treatment groups. Of the 405 subjects, 341 completed the study. The most common reason for early discontinuation was adverse events (AEs).

The primary efficacy endpoint was the change from baseline at week 16 in 6-MWD (*see* Figure 1 for results). In the tadalafil 40 mg treatment group, the placebo-adjusted mean change increase in 6-MWD was 33 meters (95% C.I. 15-50 meters; p=0.0004). The improvement in 6-MWD was apparent at 8 weeks of treatment and then maintained at week 12 and week 16 ($p<0.05$). Statistical significance in the 6-MWD was demonstrated at week 12 when subjects were asked to delay taking study medication in order to reflect trough drug concentrations.

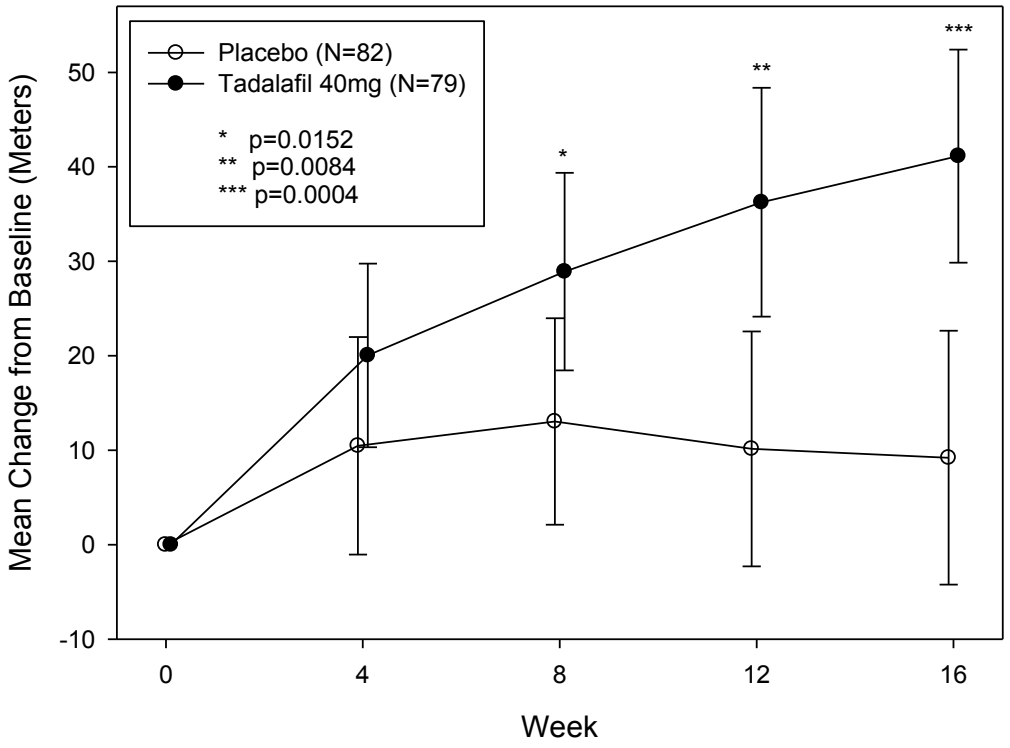
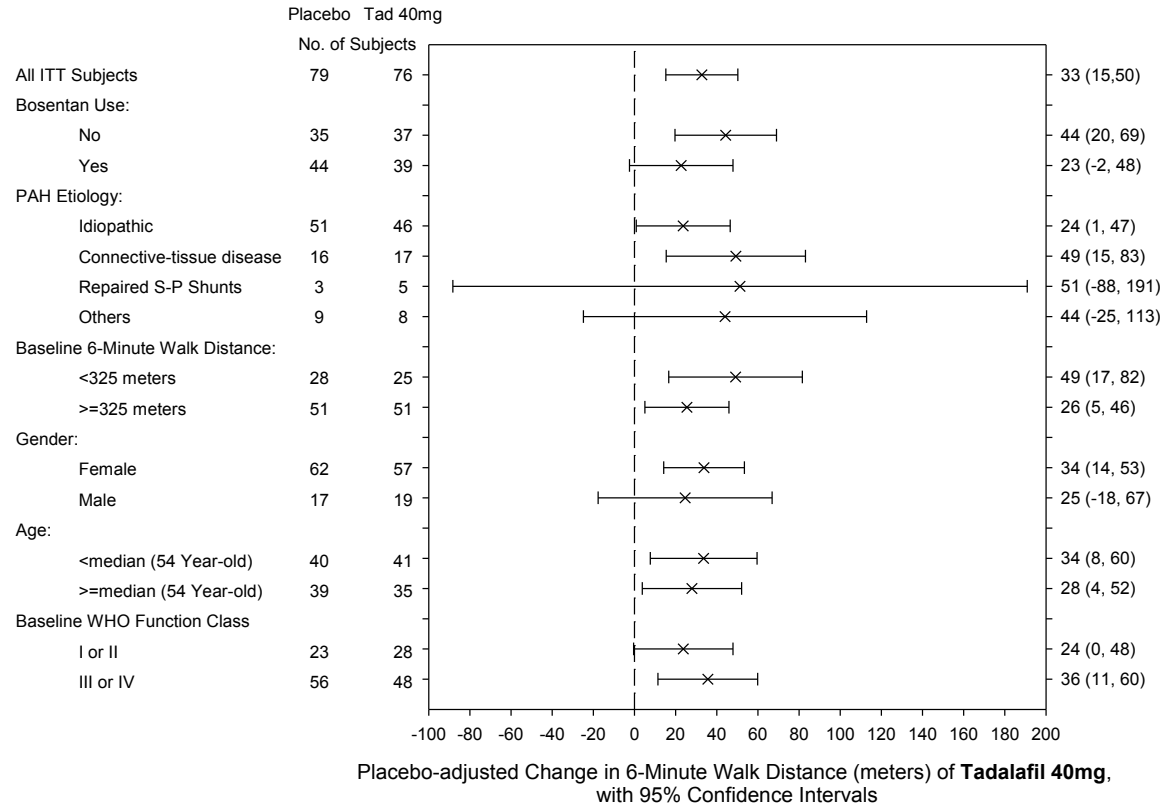


Figure 1: 6-Minute Walk Distance (meters) Mean Change from Baseline, with 95% Confidence Interval

Placebo-adjusted changes in 6-MWD at 16 weeks were evaluated in pre-defined subpopulations (s*ee* Figure 2). In patients taking only tadalafil 40 mg (i.e., without concomitant bosentan), the placebo-adjusted change in 6-MWD was 44 meters ($p<0.01$). In patients taking tadalafil 40 mg and concomitant bosentan therapy the placebo adjusted change in 6-MWD was 23 meters ($p>0.05$).



Repaired S-P Shunts=Repaired Congenital systemic-to-pulmonary shunt.

Figure 2: Placebo-adjusted Change in 6-Minute Walk Distance (meters) of Tadalafil 40 mg, with 95% Confidence Intervals

Per the protocol, the secondary endpoints were tested in the order listed in Table 2 with no further inferential testing once a statistically non-significant result was reached. Inferential testing did not process beyond WHO functional Class since this comparison was statistically non-significant. In the tadalafil 40 mg group 23% of subjects improved and 10% worsened their WHO functional class. In the placebo group 21% of subjects improved and 16% worsened their WHO functional class. The probability of having no clinical worsening was 94% with tadalafil 40 mg and 84% with placebo. Based on the number of subjects, this represents a 68% relative risk reduction in the incidence of clinical worsening (95% Confidence Interval 6% to 89%). The changes in the Borg dyspnea scores were small with both placebo and tadalafil 40 mg.

Table 2. Assessment of Secondary Endpoints in Patients with Pulmonary Arterial Hypertension Following a Randomized, Double-Blind, 16-Week Placebo-Controlled Study

	ADCIRCA 40 mg (N=79)	Placebo (N=82)
Change in WHO Functional Class No. (%)		
Improved	18 (22.8)	17 (20.7)
No Change	53 (67.1)	52 (63.4)
Worsen	8 (10.1)	13 (15.9)
Clinical Worsening[a]		
Probability of No Clinical Worsening at Week 16 (95% C.I.)	0.94 (0.85, 0.98)	0.84 (0.74, 0.90)
Number of patients (%) with Clinical Worsening	4 (5.1)	13 (15.9)
Change in Borg Dyspnea[b] **Score**		
Mean (SD)	-0.70 (1.75)	0.41 (1.89)

[a] Clinical worsening was defined as death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy, and worsening WHO functional class.

[b] A positive change in Borg-Dyspnea score represents a worsening of patient perceived breathlessness during the 6 minute walk.

A statistically significant increase in quality of life, compared to placebo, was demonstrated in the tadalafil 40 mg group in 6 of the 8 SF36 domains: physical functioning, role-physical, bodily pain, general health, vitality and social functioning domains of the SF-36 ($p<0.01$). No improvements were observed in the role emotional and mental health domains of the SF-36. Improvements compared to placebo were observed with tadalafil 40 mg in the EuroQol (EQ-5D) US and UK index scores ($p<0.001$) comprising mobility, self-care, usual activities, pain/discomfort, anxiety/depression components, and in the visual analogue scale (VAS) ($p<0.05$).

Long Term Treatment of Pulmonary Arterial Hypertension

357 patients from the placebo-controlled study entered a long-term extension study. Of these, 266 patients have been treated with tadalafil for at least 6 months and 125 for 1 year (median exposure 279 days; range 2 days to 400 days). The interim mortality rate in the extension study was 4.6 per 100 patient years. Additionally, 6 minute walk distance and WHO functional class status appeared to be stable in those treated with ADCIRCA for 1 year. Without a control group, these data must be interpreted cautiously.

DETAILED PHARMACOLOGY

General

Phosphodiesterases (PDEs) are a diverse family of enzymes having different tissue distributions and functions, but which all ultimately act to hydrolyze cyclic nucleotides, thereby terminating their actions. There are eleven known phosphodiesterase classes, many with subtypes identified by structure and function. Phosphodiesterase type 5 (PDE5) is a major cGMP-hydrolyzing enzyme in the pulmonary vasculature.

Studies *in vitro* have shown that tadalafil is a potent inhibitor of PDE5. PDE5 is an enzyme found in pulmonary vascular smooth muscle, visceral smooth muscle, corpus cavernosum, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas. The effect of tadalafil is more selective on PDE5 than on other phosphodiesterases. Tadalafil is > 10,000-fold more selective for PDE5 than for PDE1, PDE2, PDE4, and PDE7 enzymes, which are found in the heart, brain, blood vessels, liver, and other organs. Tadalafil is > 10,000-fold more selective for PDE5 than for PDE3, an enzyme found in the heart and blood vessels. This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 9000-fold more potent for PDE5 than for PDE8 through 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. 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.

TOXICOLOGY

Tadalafil has been evaluated in a comprehensive series of toxicology studies, including *in vitro* and *in vivo* genetic toxicology assays; single-dose studies in mice and rats using both oral and intravenous routes of administration; repeated-dose studies in mice, rats, and dogs; reproductive and developmental studies in rats and mice; and oncogenicity studies in rats and mice.

Tadalafil demonstrated low acute oral toxicity in both mice and rats, as doses up to 2000 mg/kg did not cause death and produced only minimal clinical observations. Daily oral administration of tadalafil to mice for 3 months at doses up to 800 mg/kg/day produced no deaths or treatment-related findings. In rats, oral toxicity studies of 1 and 6 months duration, with doses up to 400 mg/kg/day, and a 3 month study with doses up to 800 mg/kg/day, produced no treatment-related deaths or substantive clinical observations. These studies yielded no gross or histopathologic findings that were considered toxicologically important.

In dogs given tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day and above, there were alterations to the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. However, in placebo-controlled studies in men who received tadalafil 10 or 20 mg daily for up to 9 months, there were no treatment-related effects on sperm concentration, sperm count, motility, or morphology. Minimal thymic and hepatic changes were observed in dogs at higher doses.

Tadalafil was not carcinogenic to rats or mice when administered for 24 months. Tadalafil was not mutagenic or genotoxic in *in vitro* bacterial and mammalian cell assays, and *in vitro* human lymphocytes and *in vivo* rat micronucleus assays. Tadalafil induces only mild ocular and dermal irritation.

There was no evidence of teratogenicity, embryotoxicity or fetotoxicity in rats or mice that received tadalafil up to 1000 mg/kg/day. In a rat pre- and postnatal development study, the no-observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18 times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats.

The preclinical results support daily administration of tadalafil to subjects with pulmonary arterial hypertension.

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PART III: CONSUMER INFORMATION

PrADCIRCA®
(tadalafil tablets)
20 mg

This leaflet is part III of a three-part "Product Monograph" published when ADCIRCA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ADCIRCA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ADCIRCA is a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

What it does:

ADCIRCA belongs to a group of medicines called phosphodiesterase type 5 inhibitors. ADCIRCA works by helping the blood vessels in your lungs to relax, allowing the flow of blood into your lungs. This results in lowering the arterial blood pressure in your lungs.

When it should not be used:

- Do not take ADCIRCA if you are taking any medicines that contain nitrates in any form (oral, sublingual [under the tongue], skin-patch, or by inhalation). Similarly, nitrates must never be used by patients who take ADCIRCA. Nitrates are found in many prescription medicines used in the treatment of angina pectoris (chest pain due to heart disease), such as nitroglycerin, isosorbide mononitrate, or isosorbide dinitrate. If nitrates have previously been prescribed to you, even though you may not have used them, or are unsure, tell your doctor.

  If you take ADCIRCA with any nitrate-containing medicines or any other nitrates (e.g., amyl nitrite "poppers"), your blood pressure could suddenly drop to a life-threatening level. You could get dizzy, faint, or even have a heart attack or stroke.

- Do not take ADCIRCA if you have had an allergic reaction in the past to tadalafil or other medications that contain tadalafil such as CIALIS®, or any of the other ingredients in ADCIRCA.

- Do not take ADCIRCA if you have had an eye disease called non-arteritic anterior ischaemic optic neuropathy (NAION) which causes a sudden decrease or loss of vision in one or both eyes.

- Do not take ADCIRCA if you are taking guanylate cyclase stimulators, such as riociguat.

What the medicinal ingredient is:

Tadalafil

What the nonmedicinal ingredients are:

Croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

What dosage forms it comes in:

ADCIRCA is supplied as 20 mg orange, film-coated tablets. They are in the shape of almonds and have "4467" marked on one side. Each tablet of ADCIRCA contains 20 mg of tadalafil.

WARNINGS AND PRECAUTIONS

Before taking ADCIRCA talk to your doctor if you have or had any of the following conditions:

- a disease called pulmonary veno-occlusive disease (PVOD)
- lose a large amount of body fluids (dehydration). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot or don't drink enough liquids.
- heart disease or previously had a heart attack. Patients who experience chest pain or shortness of breath after taking ADCIRCA should not use nitrates and should seek immediate medical attention.
- stroke.
- low blood pressure or uncontrolled high blood pressure.
- liver or kidney problem.
- sickle cell anemia (an abnormality of red blood cells), multiple myeloma (cancer of the bone marrow), or leukemia (cancer of the blood cells).
- deformation of the penis.
- ever had severe loss of vision, including a condition called Non-Arteritic Ischemic Optic Neuropathy (NAION). The specific type of vision decrease or loss known as NAION has been reported rarely after the intake of ADCIRCA or other PDE5 inhibitors. Vision decrease or loss may be partial or complete, in one or very occasionally in both eyes. While in some cases the condition may improve over time, it can also be irreversible. If you are taking ADCIRCA and experience temporary or permanent loss or change in vision, immediately call your doctor.
- retinitis pigmentosa, a rare genetic eye disease.
- are pregnant or planning to become pregnant. It is not known if ADCIRCA could harm your unborn baby.

- are breastfeeding. It is not known if ADCIRCA passes into your breast milk or if it could harm your baby.

Long-term studies have shown that ADCIRCA therapy may decrease sperm concentration in some men. The relevance of this effect on fertility in men is unknown.

Sudden decrease or loss of hearing:

Sudden decrease or loss of hearing has been reported in a few postmarketing and clinical trial cases with the use of PDE5 inhibitors, including ADCIRCA. It has not been established whether these are related directly to the use of these medications or to other factors. If you experience these symptoms, call your doctor.

Use in children:

ADCIRCA is not intended for use in patients under 18 years of age.

Information for patients intolerant of lactose, one of the ingredients of ADCIRCA:

ADCIRCA contains a small amount of lactose (about 250 mg), which is unlikely to affect you.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicine, including medicines you can buy without prescription and natural health products.

Drugs that may interact with ADCIRCA include:
- nitrates (see previous section)
- rifampin (an antibacterial product used against tuberculosis)
- ketoconazole or itraconazole (used against fungal infections)
- erythromycin (an antibacterial product)
- protease inhibitors such as ritonavir and saquinavir (HIV treatments)
- phenobarbital, phenytoin, carbamazepine.

Tell your doctor if you are taking:
- medicines to treat high blood pressure
- alpha-blockers (such as doxazosin) for the treatment of prostate problems.

The combination of these medicines with ADCIRCA may add to the blood-pressure-lowering effect of these drugs.

- Grapefruit juice may affect ADCIRCA blood levels.

You should not use ADCIRCA together with CIALIS or any other treatments for erectile dysfunction (impotence).

PROPER USE OF THIS MEDICATION

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

How To Take ADCIRCA:

Always take ADCIRCA exactly as your doctor has instructed you. Do not take a higher dose than the one which your doctor prescribed for you. Check with your doctor or pharmacist if you are unsure.

ADCIRCA is a tablet you take by mouth. Take 2 ADCIRCA tablets together (to provide a 40 mg dose) at the same time every day. DO NOT divide the dose over the course of the day.

You may take ADCIRCA with or without food.

Alcohol consumption may temporarily decrease blood pressure.

Overdose:

If you take too much ADCIRCA, call your doctor or poison control center, or go to an emergency room.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is close to your next dose, skip the missed dose, and take your next dose at the regular time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ADCIRCA can have some side-effects. These effects are usually mild to moderate in nature.

The most common side effects are headache, muscle pain, facial flushing, nausea, pain in the arms or legs, back pain, upset stomach or heartburn, stuffy or congested nose. If you have any of these side-effects and they are troublesome, severe, or do not go away, tell your doctor.

Allergic reactions (including skin rashes) could occur.

In rare instances it is possible that a prolonged and possibly painful erection may occur after taking ADCIRCA.

If you have such an erection which lasts continuously for more than 4 hours, you should contact a doctor immediately. If this is not treated immediately, permanent penile tissue damage and erectile dysfunction may result.

Sudden decrease or loss of vision has occurred rarely after the use of oral erectile dysfunction medications, including ADCIRCA. People who have previously experienced a type of vision loss called Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) may be at an increased risk of

reoccurrence of NAION. If you experience reduction or loss of vision in one or both eyes, immediately call your doctor.

In case of chest pain or shortness of breath you should NOT use nitrates but you should seek immediate medical assistance.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Common			
Headache	✓		
muscle pain	✓		
facial flushing	✓		
back pain	✓		
indigestion	✓		
nasal congestion	✓		
Uncommon			
Swelling of eyelids	✓		
eye pain	✓		
allergic reaction	✓		
prolonged erection		✓	
chest pain		✓	
vision loss		✓	
hearing loss		✓	
temporary memory loss (transient global amnesia)		✓	

This is not a complete list of side effects. For any unexpected effects while taking ADCIRCA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store your tablets at 15 to 30°C.

Store in the original package.

Do not use after the expiry date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- **Fax toll-free to 1-866-678-6789, or**
- **Mail to: Canada Vigilance Program**
  Health Canada
  Postal Locator: 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at www.lilly.ca.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

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This leaflet was prepared by Eli Lilly Canada Inc, Toronto Ontario, M1N 2E8.

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