HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCIRCA safely and effectively. See full prescribing information for ADCIRCA.

ADCIRCA (tadalafil) tablets for oral administration

Initial U.S. Approval: 2003

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

Warnings and Precautions (5.5) 05/2017

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

ADCIRCA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%). (1.1)

----------DOSAGE AND ADMINISTRATION----------

- 40 mg once daily, with or without food. (2.1)
- Dividing the dose (40 mg) over the course of the day is not recommended. (2.1)
- Use with ritonavir requires dosage adjustments. (2.3)

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

Tablets (not scored): 20 mg (3)

----------CONTRAINDICATIONS----------

- Concomitant organic nitrates (4.1)
- Concomitant Guanylate Cyclase (GC) Stimulators (4.2)
- History of known serious hypersensitivity reaction to ADCIRCA or CIALIS (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Cardiovascular effects: Carefully consider whether patients with certain underlying conditions (e.g., cardiovascular disease, impaired autonomic control of blood pressure, aortic stenosis) could be adversely affected by vasodilatory effects of ADCIRCA. Not recommended in patients with pulmonary veno-occlusive disease. (5.1)
- Concomitant alpha-blockers or alcohol: Note additive blood pressure-lowering effects. (5.1)
- Use with Ritonavir: Requires dosage adjustment. (2.3, 5.2)
- Other concomitant potent CYP3A inhibitors: Avoid use with ADCIRCA. (5.2)
- Potent Inducers of CYP3A: Avoid use of ADCIRCA in patients chronically taking potent inducers of CYP3A (e.g., rifampin). (5.2, 7.2)
- Effects on the eye: Patients should seek immediate medical attention if sudden loss of vision occurs, which could be a sign of non-arteritic ischemic optic neuropathy (NAION). (5.5)
- Hearing impairment: Advise patients to seek immediate medical attention if sudden decrease or loss of hearing occurs. (5.6)
- Concomitant PDE5 inhibitors: Avoid use with CIALIS or other PDE5 inhibitors. (5.7)
- Prolonged erection: Advise patients to seek emergency treatment if an erection lasts >4 hours. (5.8)

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

The most common adverse reaction is headache. (6.1)

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

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

Renal Impairment (2.2, 5.3, 8.6, 12.3)
- Mild or moderate: Start with 20 mg once daily. (2.2, 5.3, 8.6)
- Severe: Avoid use of ADCIRCA. (2.2, 5.3, 8.6)

Hepatic Impairment (2.2, 5.4, 8.7, 12.3)
- Mild or moderate: Consider starting dose of 20 mg once daily. (2.2, 5.4, 8.7)
- Severe: Avoid use of ADCIRCA. (2.2, 5.4, 8.7)

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

Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

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

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

ADCIRCA® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

2 DOSAGE AND ADMINISTRATION

2.1 Pulmonary Arterial Hypertension

The recommended dose of ADCIRCA is 40 mg (two 20 mg tablets) taken once daily with or without food. Dividing the dose (40 mg) over the course of the day is not recommended.

2.2 Use in Special Populations

Renal Impairment

- Mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min): Start dosing at 20 mg once daily. Increase to 40 mg once daily based on individual tolerability.
- Severe (creatinine clearance <30 mL/min and on hemodialysis): Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Hepatic Impairment

- Mild or moderate (Child Pugh Class A or B): Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once per day.
- Severe (Child Pugh Class C): Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]*.

Geriatric Patients

- No dose adjustment is required in patients >65 years of age without renal impairment or hepatic impairment.

2.3 Use with Ritonavir

Co-administration of ADCIRCA in Patients on Ritonavir

In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability *[see Warnings and Precautions (5.2), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Co-administration of Ritonavir in Patients on ADCIRCA

Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability *[see Warnings and Precautions (5.2), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

20 mg, orange, film-coated, almond-shaped tablets (not scored) debossed with “4467”.

4 CONTRAINDICATIONS

4.1 Concomitant Organic Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway *[see Clinical Pharmacology (12.2)]*.

4.2 Concomitant Guanylate Cyclase (GC) Stimulators

Do not use ADCIRCA in patients who are using a GC stimulator, such as riociguat. ADCIRCA may potentiate the hypotensive effects of GC stimulators.

4.3 Hypersensitivity Reactions

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

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.

PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient

autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

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.

There is a lack of data on safety and efficacy in the following groups who were specifically excluded from 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

Use with Alpha Blockers and Antihypertensives

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are vasodilators with blood pressure–lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs *[see Drug Interactions (7.1)]*.

Use with Alcohol

Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5.2 Use with Potent CYP3A Inhibitors or Inducers

Co-administration of ADCIRCA in Patients on Ritonavir

In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability *[see Dosage and Administration (2.3), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Co-administration of Ritonavir in Patients on ADCIRCA

Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability *[see Dosage and Administration (2.3), Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5.3 Use in Renal Impairment

In patients with mild or moderate renal impairment

Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

In patients with severe renal impairment

Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

5.4 Use in Hepatic Impairment

In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCIRCA *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

In patients with severe hepatic cirrhosis (Child-Pugh Class C)

Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

5.5 Visual Loss

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 postmarketing in temporal association with

development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥50 in the general population. An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, typical of erectile dysfunction treatment, 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 (6.2)].*

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.

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

5.6 Hearing Impairment

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 (6.2)]*.

5.7 Combination with Other PDE5 Inhibitors

Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

5.8 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.

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

5.9 Effects on Bleeding

PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions (5.1)]*
- Visual Loss *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*
- Hearing loss *[see Warnings and Precautions (5.6)]*
- Priapism *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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

Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.

In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

Table 1: Treatment-Emergent Adverse Events Reported by ≥9% of Patients in ADCIRCA and More Frequent than Placebo by 2%

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Headache	15	32	42
Myalgia	4	9	14
Nasopharyngitis	7	2	13
Flushing	2	6	13
Respiratory Tract Infection (Upper and Lower)	6	7	13
Pain in Extremity	2	5	11
Nausea	6	10	11
Back Pain	6	12	10
Dyspepsia	2	13	10
Nasal Congestion (Including sinus congestion)	1	0	9

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.

Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors *[see Warnings and Precautions (5.1)]*.

Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis

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

Ophthalmologic — Visual field defect, retinal vein occlusion, retinal artery occlusion, and NAION *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)].*

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 some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors *[see Warnings and Precautions (5.6) and Patient Counseling Information (17)]*.

Urogenital — Priapism *[see Warnings and Precautions (5.8)]*.

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with ADCIRCA

Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate *[see Contraindications (4.1)]*. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates *[see Clinical Pharmacology (12.2)]*. 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.

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 Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

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, bendroflumethiazide, enalapril, and

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.