

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
Regence BlueCross BlueShield of Utah • Regence BlueShield of Idaho
Independent licensees of the Blue Cross and Blue Shield Association**

Medication Policy Manual

Policy No: dru184

Topic: Adcirca™ (tadalafil) 20 mg

Date of Origin: June 29, 2009

Revised/Effective Date: July 17, 2009

Next Review Date: July 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Adcirca™ (tadalafil) is an oral medication used in the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity. Tadalafil is also the active ingredient in Cialis®, used in the treatment of erectile dysfunction. While Cialis is available as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets, Adcirca (tadalafil) is available as a 20 mg tablet and is dosed at 2 tablets (40 mg) given once daily for the treatment of PAH. Adcirca (tadalafil) should not be used in the treatment of erectile dysfunction.

Policy/Criteria

- I.** Most contracts require prior authorization approval of Adcirca (tadalafil) prior to coverage. Adcirca (tadalafil) may be considered medically necessary for the treatment of pulmonary arterial hypertension (PAH).

- II.** Administration, Quantity Limitations, and Authorization Period
 - A.** Regence considers Adcirca (tadalafil) to be a self-administered medication.
 - B.** When prior authorization is approved, Adcirca (tadalafil) may be authorized in quantities of sixty (60), 20-mg tablets per month.
 - C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Adcirca (tadalafil) is considered investigational when used for all other conditions, including but not limited to:
 - A.** Erectile dysfunction.
 - B.** Reynaud's phenomenon.

Position Summary

Summary

- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan), and type 5 phosphodiesterase inhibitors (sildenafil, tadalafil).
- In early disease or with less severe symptoms, oral therapies may be used. As symptoms progress, injectable therapies, such as epoprostenol and treprostinil, become necessary.
- Adcirca (tadalafil) 40 mg is used in the treatment of patients with pulmonary arterial hypertension. It has been shown to improve exercise tolerance in this patient population.^[1]

- There are currently no trials of adequate design or of sufficient duration that demonstrate improved survival with Adcirca (tadalafil) in patients with PAH.
- Both sildenafil and tadalafil have been studied individually in the treatment of PAH. To date, there is no evidence that either one of these products is more effective than the other.
- Tadalafil is also the active ingredient in Cialis. Cialis is used for the treatment of erectile dysfunction and is available as 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. ^[2]
- Adcirca (tadalafil 40 mg daily) has not been studied in the treatment of erectile dysfunction. Its use in this condition is therefore considered investigational.

Clinical Efficacy

- In a single unreliable pivotal trial in 405 patients with PAH: ^[1]
 - * Adcirca (tadalafil) 40 mg once daily improved exercise capacity at 16-weeks compared to placebo, based on a six-minute walking distance test. The six-minute walk test measures the distance that is covered in a 6-minute timeframe. Improvements in this test have been correlated to improved survival in PAH patients.
 - * Patients using Adcirca (tadalafil) 40 mg once daily were less likely to show clinical worsening than those taking placebo or patients treated with lower doses of Adcirca. Clinical worsening was (defined as death, lung transplantation, atrial septostomy, hospitalization for worsening PAH, new PAH therapy, or worsening WHO functional class. World Health Organization (WHO) functional class) is a measure of the level of physical activity that is tolerated without symptoms. It ranges from functional class I where no limitations to physical activity are present, to functional class IV where symptoms are present at rest).
- Results of this trial may not be reliable due to flaws that included a dropout rate of approximately 15%. Also, some subjects may have been allowed to take other medications for PAH, such as bosentan (Tracleer). These other medications may have contributed to the differences that were observed between groups.

Safety

- Safety data for Adcirca (tadalafil) 40 mg is limited to adverse events described in the 16-week pivotal trial and an open-label, non-comparator extension trial of up to one year. ^[1]

- The most common side effects reported ($\geq 9\%$ patients) were headache (42%), myalgia (14%), nasopharyngitis (13%), flushing (13%), and respiratory tract infection (13%).^[1] (The statistical significance of these adverse events versus placebo was not reported).
- Use of Adcirca (tadalafil) with any form of organic nitrates (eg. nitroglycerin, isosorbide dinitrate) is contraindicated.^[1]
- Use of Adcirca (tadalafil) with potent CYP3A4 inhibitors or inducers (see *Appendix I*) may substantially alter serum levels of tadalafil and is not recommended.^[1]
- Use of Adcirca (tadalafil) with alcohol, alpha-blockers (eg. terazosin, doxazosin), or other PDE-5 inhibitors (eg. sildenafil, vardenafil) should be avoided.^[1]

Administration and Dosing

- The recommended dose of Adcirca (tadalafil) for the treatment of PAH is 40 mg once daily. It is not recommended that this dose be divided up over the course of the day.^[1]
- Use of Adcirca (tadalafil) with ritonavir requires dose-adjustment.^[1]

Use of Adcirca (tadalafil) in Other Conditions

- Other potential uses of Adcirca (tadalafil) include the treatment of erectile dysfunction and the treatment of Reynaud's phenomenon.
 - * Tadalafil (Cialis[®]) 20 mg is FDA-approved dose for the treatment of erectile dysfunction.^[2]
 - * A small (n = 20) placebo-controlled, cross-over study of patients with primary or secondary Reynaud's phenomenon found no significant difference in digital blood flow between patients receiving a single dose of tadalafil and those receiving placebo.^[3] Larger, better designed studies are needed to establish tadalafil as safe and effective for the treatment of Raynaud's.

Appendix I: CYP3A Inhibitors and Inducers

Potent Inhibitors of CYP3A ^[4]	
amiodarone (Cordarone [®] , Pacerone [®]) atazanavir (Reyataz [®]) cisapride (Propulsid [®]) clarithromycin (Biaxin [®]) indinavir (Crixivan [®]) itraconazole (Sporanox [®]) ketoconazole (Nizoral [®])	nefazodone (Serzone [®]) nelfinavir (Viracept [®]) ritonavir (Norvir [®]) telithromycin (Ketek [®]) troleandomycin (TAO [®]) voriconazole (Vfend [®])
Inducers of CYP3A ^[5]	
rifampin (Rifadin [®]) phenobarbital (generic) carbamazepine (generic) clotrimazole (generic)	dexamethasone (generic) phenytoin (generic) sulfipyrazone (Canadian drug)

References

1. Adcirca™ (tadalafil) tablets prescribing information. Eli Lilly and Company: Indianapolis, IN; May 2009.
2. Cialis® (tadalafil) tablets prescribing information. Eli Lilly and Company: Indianapolis, IN; Nov 2003.
3. Friedman EA, Harris PA, Wood AJ, Stein CM, Kurnik D. The effects of tadalafil on cold-induced vasoconstriction in patients with Raynaud's phenomenon. *Clin Pharmacol Ther.* 2007 Apr;81(4):503-9. Epub 2007 Feb 14.
4. CYP3A and Drug Interactions. *The Medical Letter.* Volume 47 (issue 1212), July 4, 2005.
5. Liu YT, Hao HP, Liu CX, Wang GJ, Xie HG. Drugs as CYP3A probes, inducers, and inhibitors. *Drug Metab Rev.* 2007;39(4): 699-721.

Cross References
Treatment of pulmonary hypertension with prostacyclin analogues, endothelin receptor antagonists, or phosphodiesterase inhibitors, BlueCross BlueShield Association Medical Policy, 5.01.09, Issue 4.2009.
Cialis®, tadalafil dru099
Levitra®, vardenafil dru096
Revatio®, sildenafil dru117
Viagra®, sildenafil dru024

Codes	Number	Description
N/A		