

Tadalafil (Adcirca®)

Issued by PHA's Scientific Leadership Council

Information is based on the United States Food and Drug Administration drug labeling

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WHAT IS TADALAFIL?

Tadalafil is an oral medication called a phosphodiesterase-5 (PDE5) inhibitor approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Group 1 patients. The goal of this therapy is to improve exercise ability and delay clinical worsening. Research studies showing the effectiveness of the medication included mostly patients with symptoms that were rated as WHO Functional Class II-III.

Tadalafil is marketed as Adcirca® for PAH and was approved by the United States Food and Drug Administration (FDA) in 2009. Tadalafil is also marketed as Cialis® for erectile dysfunction but not for the treatment of PAH.

HOW DOES TADALAFIL WORK?

PDE5 is a substance produced in the lungs and other parts of the body that breaks down another substance called cyclic guanosine monophosphate (GMP). Cyclic GMP causes the blood vessels (arteries) to relax and widen. Tadalafil decreases the activity of PDE5, so that more cyclic GMP is available for the blood vessels inside the lungs. This leads to relaxation, or widening, of those vessels. Relaxing and widening of the blood vessels in the lungs decreases the pulmonary blood pressure to the heart and improves its function. This reduces blood pressure in the lungs which generally results in the ability to be more active. Research studies have verified this improvement

HOW IS TADALAFIL GIVEN?

The recommended dose of tadalafil for the treatment of PAH is 40 mg (two 20 mg tablets) once daily with or without food. Your physician may have you begin with one tablet a day and then advance to the full dose of two tablets daily to allow you to adjust to the medication.

HOW IS TADALAFIL SUPPLIED?

Tadalafil is available as an orange, almond-shaped 20 mg pill.

HOW CAN A PATIENT OBTAIN TADALAFIL?

Tadalafil must be prescribed by a physician, and insurance approval must be obtained prior to starting therapy. It is carried by most retail and specialty pharmacies, including Accredo Health Inc., Aetna Specialty Pharmacy, CVS Caremark, Cigna Tel-Drug, CuraScript, Kaiser Permanente Specialty Pharmacy, Precision Rx, Walgreens Specialty Pharmacy (Medmark) and WellCare.

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WILL INSURANCE PAY FOR TADALAFIL?

It is expected that most health insurance plans will pay part of the cost of this medication. However, some plans still leave patients with a high out-of-pocket responsibility.

Depending on your insurance type, you may be eligible for assistance from the company that manufactures your therapy or from a non-profit charitable assistance organization. For more information visit www.PHAssociation.org/Help or call 301-565-3004.

WHAT ARE THE FREQUENT SIDE EFFECTS OF TADALAFIL?

Tadalafil is generally well tolerated. The most frequent side effects are:

- Headache
- Muscle pain
- Nasal stuffiness
- Flushing of the skin
- Respiratory infection
- Leg or arm pain
- Nausea
- Back pain
- Upset stomach

A reduction in blood pressure throughout the body may occur because tadalafil relaxes blood vessels (arteries) throughout the body. Caution must be used in patients with low blood pressure - for example, less than 90/50 mmHg. Caution is also needed in patients with dehydration, left-sided heart diseases and certain abnormalities of the body's nervous system function.

Taking certain medications such as nitrates, nitric oxide donors or alpha blockers along with tadalafil can cause a significant drop in blood pressure. This could result in loss of consciousness or even death. You should make certain that you are not taking these medications before starting tadalafil. Use of tadalafil with medications known as nitrates is **CONTRAINDICATED**.

Prolonged erection (greater than four hours) in a male patient is a rare but very serious side effect; if this should happen to you, you should go to an emergency room or contact your doctor immediately.

Sudden loss of vision in one or both eyes has occurred in patients on PDE5 inhibitors. Such an event may represent serious dysfunction of the optic nerve and requires immediate medical attention.

Sudden loss of hearing may occur and may be accompanied by dizziness and/or ear ringing. Patients should seek prompt medical attention should this occur.

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HOW ARE SIDE EFFECTS OF TADALAFIL MONITORED?

No regular bloodwork for side effects is required. Your doctor may ask you to monitor your blood pressure on a regular basis particularly during your first few days on treatment or with a dose increase. Blood pressure monitoring is not needed for most patients.

If you experience any of the symptoms mentioned in the previous section, you should promptly notify your physician.

WHAT ARE CONSIDERATIONS FOR USE OF TADALAFIL IN SPECIAL POPULATIONS?

The safety and effectiveness of tadalafil in pediatric PAH patients has not been established.

Tadalafil does not exhibit harm to the fetus in animal studies; however, it has not been studied in pregnant or nursing women. As there are no adequate and well-controlled human studies, tadalafil should be used in pregnancy only if clearly needed, and caution should be exercised in nursing women.

There is limited experience using tadalafil in patients with liver disease. In mild or moderate liver disease (Child Pugh Class A or B), one should consider starting tadalafil at a dose of 20 mg once daily. In severe liver disease (Child Pugh Class C), it is generally recommended to avoid use.

In patients with mild-to-moderate kidney disease (creatinine clearance 31 to 80 ml/min), it is recommended to start tadalafil at 20 mg once daily and to increase to 40 mg once daily based on individual tolerability. In patients with severe kidney disease (creatinine clearance < 30 ml/min or on dialysis), it is recommended to avoid use of tadalafil. This is because severe kidney disease increases the amount of tadalafil in the bloodstream, even in patients on dialysis. Also, there is limited experience using tadalafil in these patients.

Tadalafil is not recommended in patients with either of two rare diseases often associated with PAH: pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.

COULD A PATIENT BE ALLERGIC TO TADALAFIL?

This is possible, but not likely.

WHAT ARE IMPORTANT DRUG INTERACTIONS WITH TADALAFIL? (PLEASE SEE PACKAGE INSERT FOR FULL DETAILS)

Tadalafil should not be used in combination with nitrates or nitric oxide donors as an unsafe drop in systemic blood pressure may occur.

Caution should be used if tadalafil is to be used in combination with either alcohol or anti-hypertensive medications. Tadalafil is broken down predominantly by an enzyme called CYP3A in the liver; therefore, important interactions may occur with medications that affect this enzyme pathway. Simultaneous use of bosentan and tadalafil may result in decreased tadalafil blood levels. However, changes in the usual dosing of these two medications when used in

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combination are not typically necessary.

Patients with human immunodeficiency virus (HIV or AIDS), who are taking medicines called antiretroviral agents, should not use a phosphodiesterase inhibitor such as tadalafil since it can dramatically impair the efficacy of the antiretroviral.

MISCELLANEOUS CONSIDERATIONS:

IS THERE ANY RISK OF BLINDNESS WHEN USING TADALAFIL?

There have been rare reports of blindness with use of all the currently available PDE5 inhibitors, including tadalafil. This type of blindness, which may be permanent, is called non-arteritic anterior ischemic optic neuropathy (NAION). It is not yet clear whether this is related to the use of tadalafil or to the underlying cardiovascular diseases that place the persons at risk for this particular type of blindness, even in the absence of tadalafil use.

There is no research to determine whether use of tadalafil is beneficial or safe in patients with retinitis pigmentosa, and use in these patients is not recommended.

As noted above, patients taking tadalafil should seek immediate medical attention in the event of sudden vision loss.

CAN MEN AND WOMEN TAKE TADALAFIL?

Yes, studies have evaluated tadalafil in both men and women with PAH, and no differences in side effects have been reported. Studies have not shown any effect on sexual function in women who have taken tadalafil.