



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Oral Phosphodiesterase-5 Inhibitors for PAH (Revatio[®], Adcirca[®])

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Revatio[®] is a preferred brand oral phosphodiesterase-5 inhibitor product.

CIGNA covers sildenafil (Revatio[®]) as medically necessary for the treatment of WHO Group 1 pulmonary arterial hypertension (PAH) to improve exercise ability and delay clinical worsening.

Adcirca[®] is a non-preferred brand oral phosphodiesterase-5 inhibitor product.

CIGNA covers tadalafil (Adcirca[®]) as medically necessary for the treatment of WHO Group 1 pulmonary arterial hypertension (PAH) to improve exercise ability and delay clinical worsening **ONLY** when there is a failure, contraindication, or intolerance to sildenafil (Revatio[®]).

FDA Approved Indication

Revatio

Revatio is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

Adcirca

Adcirca is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

FDA Recommended Dosing

Revatio

Tablets - The recommended dose is 20 mg three times a day (TID). Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

Injection - Revatio injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral Revatio and who are temporarily unable to take oral medication. The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose does not need to be adjusted for body weight. A 10 mg dose injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

Adcirca

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

Drug Availability

Revatio

Tablets - Revatio tablets are supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as 20mg in a bottle of 90 tablets.

Injection – Revatio Injection is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg sildenafil (12.5mL) presented in a glass vial.

Adcirca

Adcirca (tadalafil) is supplied as 20 mg orange, film-coated, almond-shaped tablets (not scored), debossed with “4467” in bottles of 60 tablets.

General Background

Disease Overview

Primary Pulmonary Hypertension (PPH) is a rare disorder with a female predominance. Without therapy, the prognosis is poor, with an estimated median life expectancy of 2.8 years from the time of diagnosis. PPH was defined by the National Institutes of Health (NIH) registry working-group as a mean pulmonary artery pressure of > 25 mm Hg at rest or 30 mm Hg with exercise and no proven underlying etiology. The World Health Organization (WHO) symposium on PPH defined this entity as a systolic pulmonary artery pressure > 40 mm Hg with a tricuspid regurgitation jet of 3–3.5 m/s by Doppler in the absence of secondary causes. It is of paramount importance to distinguish Pulmonary Arterial Hypertension (PAH) from other types of pulmonary hypertension (PH). The WHO classification of PH is outlined in Table 1. PH due to other causes is thought to differ pathophysiologically from PAH, and is generally managed differently, always with a focus on the underlying cause.

Table 1 – Pulmonary Arterial Hypertension (PAH) WHO Clinical Classification System

Group 1	Pulmonary arterial hypertension (PAH)
	<ul style="list-style-type: none">• Idiopathic (IPAH)• Familial (FPAH)• Associated with (APAH)<ul style="list-style-type: none">○ Connective tissue disease○ Congenital systemic-to-pulmonary shunts○ Portal hypertension○ HIV infection○ Drugs and toxins○ Other (thyroid disorders, glycogen storage disease,

	<p>Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)</p> <ul style="list-style-type: none"> • Associated with significant venous or capillary involvement <ul style="list-style-type: none"> ○ Pulmonary veno-occlusive disease (PVOD) ○ Pulmonary capillary haemangiomatosis (PCH) • Persistent pulmonary hypertension of the newborn (PPHN)
Group II	Pulmonary hypertension associated with left heart diseases
Group III	Pulmonary hypertension associated with respiratory diseases and / or hypoxemia (including chronic obstructive pulmonary disease)
Group IV	Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group V	Miscellaneous group (eg. sarcoidosis, histiocytosis X and lymphangiomatosis)

Pharmacology

Revatio

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature. PDE5 is an enzyme responsible for degrading cGMP in the corpus cavernosum. Therefore, sildenafil increases cGMP within pulmonary vascular smooth muscle cells, resulting in relaxation. Sildenafil is the same active ingredient found in Viagra which is used in the treatment of erectile dysfunction.

Adcirca

Tadalafil inhibits phosphodiesterase type-5, which increases cyclic guanosine monophosphate in pulmonary smooth muscle cells, thereby relaxing the pulmonary vasculature. Tadalafil peak concentrations occur between 2 and 8 hours after one dose. Tadalafil absorption is not affected by food. The drug distributes into tissues and is 94% protein-bound. Tadalafil is metabolized by CYP3A with a half-life of 35 hours in patients with PAH (15 hours in healthy patients). Tadalafil is excreted as metabolites in the feces and urine. Clearance decreases in elderly patients and in patients with renal and hepatic impairment.

Guidelines

There are five oral or inhaled agents labeled for the treatment of pulmonary arterial hypertension (PAH). The oral agents include ambrisentan, bosentan, sildenafil, and tadalafil. Current treatment guidelines from the American College of Chest Physicians (2009) recommend sildenafil as a first-line agent in NYHA class II PAH and as one of the first-line treatment in class III PAH.

The New York Heart Association (NYHA) classification system is outlined in Table 2.

Table 2 - New York Heart Association (NYHA) Classification - a functional and therapeutic classification for prescription of physical activity for cardiac patients

Class 1	patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class 2	patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
Class 3	patients with marked limitation of activity; they are comfortable only at rest
Class 4	patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Tadalafil is an oral phosphodiesterase₅ (PDE₅) inhibitor labeled to improve exercise capacity in patients with pulmonary arterial hypertension (PAH). Sildenafil (Revatio) is also a PDE₅ inhibitor labeled for this use. Clinical practice guidelines for PAH do not include tadalafil because it was not available at the time they were published.

Clinical Efficacy

Revatio

Sildenafil has similar efficacy when added to conventional therapy, although few direct comparisons are available. In controlled trials, these agents increased 6-minute walk distance up to 64% (or 114 m), reduced PAP up to 32% (or 25 mmHg), reduced dyspnea, prevented clinical worsening, and improved quality of life. Functional class improved in 14 – 60% of treated patients. Several bosentan and sildenafil trials used doses higher than those approved in the product labeling. Results are similar in patients with idiopathic or secondary PAH.

No trials have directly compared the effects of these agents on survival. However, treatment with sildenafil appears to increase survival rates nominally by 3-66% from that expected in patients with PAH, whether the specific agent is given alone or with other therapies as part of a treatment algorithm.

The following provides information on the oral PAH medications for special populations:

- **Children** - There is a published controlled trial evaluating the clinical efficacy of sildenafil in children, but only case series for bosentan and iloprost. Bosentan, inhaled iloprost, and sildenafil are effective in children with PAH, reducing mean PAP, improving 6-minute walk distance and functional class. There are no published reports of ambrisentan use in children
- **Elderly Patients** - Controlled trials for ambrisentan, bosentan, iloprost, and sildenafil included elderly patients, although not all trials reported specific results for this age subgroup. Efficacy and safety appear similar in the elderly and in younger adults for most of the agents. Although no statistical comparison was provided, ambrisentan's product labeling reports that 6-minute walk distance improved less and peripheral edema was more common in the elderly compared with younger adults
- **Pregnant Patients** - There are no controlled trials of these agents in pregnant women. Case reports or case series are available for inhaled iloprost (n = 5), oral sildenafil (n = 1), and the combination of sildenafil plus bosentan (n = 1). In most reports, symptoms and functional class worsened throughout pregnancy, regardless of the specific treatment given, dosage increases, or the addition of another agent for PAH. Mothers began therapy between 10 – 28 weeks gestation for iloprost, 28 – 31 weeks for sildenafil, and prior to conception for bosentan. All infants were well at delivery. No case reports are available for ambrisentan use in pregnancy. Both ambrisentan and bosentan are contraindicated in pregnancy, with negative pregnancy tests required before initiation and monthly during therapy.

A 12-week, multinational, double-blind, placebo-controlled study evaluated the efficacy of sildenafil in 278 patients with symptomatic pulmonary arterial hypertension (PAH), either idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts. PAH was defined as mean pulmonary arterial pressure (PAP) of > 25 mm Hg at rest with pulmonary capillary wedge pressure <15 mm Hg. Patients were randomly assigned to receive placebo or sildenafil 20 mg, 40 mg, or 80 mg three times daily for 12 weeks. The primary end point was the change from baseline to week 12 in the distance walked in six minutes. In addition, the change in mean pulmonary artery pressure and World Health Organization (WHO) functional class and the incidence of clinical worsening were also assessed. In all sildenafil-treated groups, the distance walked in six minutes increased from baseline. The mean placebo-corrected treatment effects were 45 meter (m) (+13.0%), 46 m (+13.3%), and 50 m (+14.7%) for 20, 40, and 80 mg of sildenafil, respectively (p<0.001). Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline at one year in the distance walked in six minutes was 51 m. All sildenafil doses reduced the mean pulmonary artery pressure (p=0.04, p=0.01, and p<0.001, respectively), and improved the WHO functional class (p=0.003, p<0.001, and p<0.001, respectively).

Adcirca

In a single-dose study, tadalafil improved PVR, PAP, cardiac index and pulmonary vascular resistance/systemic vascular resistance (PVR/SVR) ratio similar to sildenafil and vardenafil (p=NS between treatments). Sildenafil was superior to nitric oxide; however vardenafil and tadalafil were not. This trial studied tadalafil 20 mg, 40 mg, and 60 mg. The 60 mg dose did not confer additional benefit for PVR or mean PAP. Tadalafil reduced PVR by 19% to 27% and mean PAP by 10 to 18%. It increased cardiac index by 19% (at 60 mg dose, higher than the recommended dose) and decreased PVR/SVR ratio by 12% to 16%.

In a 16-week unpublished trial available only from the manufacturer, patients were randomized to receive tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo. More than 50% of patients in this trial were concurrently taking bosentan. Tadalafil 40 mg improved the 6-minute walking distance by 33 meters compared to placebo (95% CI, 15 to 50 meters; p=0.0004). Clinical worsening occurred in fewer patients taking tadalafil 40 mg than placebo (5% vs. 16%, p value not reported). Also, time to clinical worsening was longer in patients taking tadalafil 40 mg (specific time frames not reported; p=0.041). Six-minute walking distance results were also reported for certain subgroups. Patients who were concurrently taking bosentan improved the 6-minute walking distance by 44 meters (95% CI, 20 to 69 meters) and those not taking bosentan improved the 6-minute walking distance by 23 meters, although this result was not statistically significant (95% CI, -2 to 48 meters; p=0.09). Additional studies are needed to further define tadalafil's role in combination with bosentan therapy. Improvements of 6-minute walking distance were noted in patients with NYHA functional class II (+ 29 meters, 95% CI, 4 to 53 meters) and functional class III (+ 34 meters, 95% CI, 10 to 58 meters).¹ A long-term extension of this study followed patients on tadalafil 20 mg or 40 mg. After 44 weeks, an interim analysis reported tadalafil improved 6-minute walking distance by 38 meters compared to baseline after 44 weeks (n=213 patients; 95% CI, 29 to 47 meters). Long-term comparative studies will help further define tadalafil's role in long-term use.

Adverse Reactions/Contraindications

Revatio

Sildenafil is contraindicated with all nitrates and in patients with a known hypersensitivity to any component of the tablet. Because sildenafil has vasodilator properties, use can result in mild to transient decreases in blood pressure. Caution should be taken in patients with underlying conditions that could be affected by these vasodilatory effects.

Sildenafil and alpha-blockers, such as tamsulosin are vasodilators with blood pressure lowering effects. Concomitant use can result in symptomatic hypotension. Use caution in patients taking these medications together. The metabolism of sildenafil is primarily through cytochrome P450 3A4 (CYP3A4). Because potent 3A4 inhibitors (e.g., ketoconazole and itraconazole) strongly inhibit CYP3A4, concentrations of sildenafil may increase with co-administration. Therefore, co-administration of sildenafil with potent 3A4 inhibitors is not recommended.

Overall, sildenafil is well tolerated. The following side effects were reported in patients taking sildenafil – hypotension (low blood pressure) and more shortness of breath than usual - a doctor should be notified immediately if more shortness of breath is experienced after using sildenafil (this may be due to an underlying medical condition and not directly to the use of sildenafil). The following side effects were reported rarely in patients taking sildenafil: decreased eyesight or loss of sight in one or both eyes; sudden decrease or loss of hearing, dizziness, and/or tinnitus (ringing in the ears); heart attack, stroke, irregular heartbeats, and death (Note: most of these happened in men who already had heart problems); erections that last several hours (up to 4 hours). Report any of the preceding rare occurrences to a doctor immediately. It is not possible to determine whether these events are related directly to this class of oral medicines, including sildenafil, or to other diseases or medications, to other factors, or to a combination of factors. In clinical trials using the 20 mg three times daily dose, the most common side effects include nosebleed, headache, upset stomach, getting red or hot in the face (flushing), and trouble sleeping.

Adcirca

The most common adverse effects of tadalafil are headache, muscle pain, and flushing. Serious cardiovascular events are rare and are more likely in patients with preexisting cardiovascular disease. Concomitant use with nitrates is contraindicated. Avoid tadalafil use with potent CYP3A4 inhibitors or inducers. Increased hypotension may occur if tadalafil is given with antihypertensive agents.

Coding/Billing Information

Note: This section is not in use.

References

1. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. Jul 2004;126(1 Suppl):35S-62S.
2. Badesch DB, Abman SH, Simonneau G, Lewis JR, Vallerie VM. Medical Therapy for Pulmonary Arterial Hypertension - Updated ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2007;131;1917-1928.
3. Bendayan D, Shitrit D, Kramer MR. Combination therapy with prostacyclin and tadalafil for severe pulmonary arterial hypertension: a pilot study. *Respirology*. Nov 2008;13(6):916-918.
4. Eli Lilly and Company. Adcirca (tadalafil) Tablets Product Information. Indianapolis, IN: Eli Lilly and Company. May 2009.
5. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. Aug 2 2005;46(3):529-535.
6. Galiè N, Ghofrani H, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005 Nov;17;353(20):2148-57.
7. Ghofrani HA, Voswinckel R, Reichenberger F, et al. Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol*. Oct 6 2004;44(7):1488-1496.
8. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2010.
9. Nahata MC, Morosco RS, Brady MT. Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. *Am J Health Syst Pharm*. Feb 1 2006;63(3):254-257.
10. New York Heart Association (NYHA). Functional and therapeutic classification for prescription of physical activity for cardiac patients. Clinical Trials Networks Best Practices. Available at: <https://www.ctnbestpractices.org/sites/sitereftools/classifications/new-york-heart-association/>. Accessed on March 11, 2010.
11. New York Heart Association (NYHA). Heart Failure Classification. American Heart Association. Accessed on March 15, 2010. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=330#class>.
12. Pfizer Labs. Sildenafil (Revatio®) package insert. New York, NY: Pfizer Labs. November 2010.
13. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. Jun 16 2004;43(12 Suppl S):5S-12S.
14. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe
15. Tay EL, Geok-Mui MK, Poh-Hoon MC, Yip J. Sustained benefit of tadalafil in patients with pulmonary arterial hypertension with prior response to sildenafil: a case series of 12 patients. *Int J Cardiol*. Apr 25 2008;125(3):416-417.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	10/15/2008	6121	Sildenafil (Revatio®)

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