



CIGNA PHARMACY COVERAGE POLICY

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

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Coverage Policy Number 6121

Subject **Sildenafil (Revatio®)**

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Hyperlink to Related Coverage Policies

Flolan® (Epoprostenol), Remodulin®
(Treprostinil)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant'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 participant'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 participant'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 group 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 ©2008 CIGNA

Coverage Policy

CIGNA HealthCare covers sildenafil (Revatio®) as medically necessary for the treatment of pulmonary arterial hypertension (PAH).

General Background

FDA Approved Indications

Revatio is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. The efficacy of Revatio has not been evaluated in patients currently on bosentan therapy.

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.

There are four oral or inhaled agents labeled for the treatment of pulmonary arterial hypertension (PAH). The oral agents include ambrisentan, bosentan, and sildenafil. Current treatment guidelines from the American College of Chest Physicians (2007) recommend sildenafil as a first-line agent in NYHA class II PAH and as first-line treatment in class III PAH.

The New York Heart Association (NYHA) classification system is outlined in Table 1.

Table 1 - 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

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. Recently, 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 Doppler³ 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 2. PH due to other causes is thought to differ patho-physiologically from PAH, and is generally managed differently, always with a focus on the underlying cause.

Table 2 – 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, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy) • Associated with significant venous or capillary involvement <ul style="list-style-type: none"> ○ Pulmonary veno-occlusive disease (PVOD) ○ Pulmonary capillary haemangiomas (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)

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).

A randomized, double-blind, placebo-controlled crossover trial was conducted to study the efficacy and safety of oral sildenafil in PAH patients. A total of 20 patients with severe PAH, 10 each of idiopathic PAH (IPAH) and Eisenmenger syndrome, were enrolled. Patients randomly received placebo or sildenafil for six weeks and, after a washout period of two weeks, were crossed over. The primary end point of efficacy was the improvement in distance covered in a six-minute walk test. Secondary end points were reduction in pulmonary artery pressure as measured by Doppler echocardiography after six weeks of treatment, improvement in clinical condition, New York Heart Association (NYHA) class, and exercise duration and metabolic equivalents (METs) achieved on modified Bruce exercise protocol. Sildenafil significantly improved the symptomatic status, exercise capacity, NYHA class, and hemodynamic parameters of patients with severe PAH. The primary end point of distance covered in the six-minute walk test improved from 262 ± 99 to 358.9 ± 96.5 m after treatment with sildenafil (p<0.0001). Pulmonary artery pressure improved from the baseline of 98.8 ± 20.5 to 78.3 ± 15.3 mm Hg (p<0.0001); NYHA class improved from

2.65 ± 0.59 to 1.55 ± 0.51 (p<0.0001), exercise duration from 6.4 ± 3.1 to 10.2 ± 2.05 minutes (p<0.0001), and METS achieved from 3.32 ± 1.57 to 6.04 ± 1.87 (p<0.0001) after treatment with sildenafil. No serious side effects or significant fall in blood pressure were reported throughout the study with placebo and sildenafil.

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.

The recommended dose of sildenafil is 20 mg three times a day. Treatment with doses higher than 20 mg three times daily is not recommended.

Coding/Billing Information

Note: This section is not in use.

References

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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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