



# CIGNA MEDICAL 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.

Effective Date ..... 10/15/2010  
Next Review Date.....10/15/2011  
Coverage Policy Number ..... 4096

Subject **Epoprostenol (Flolan™)**

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## Hyperlink to Related Coverage Policies

Treprostinil (Remodulin®, Tyvaso™)

### 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 ©2010 CIGNA

## Coverage Policy

CIGNA covers epoprostenol (Flolan™) as medically necessary for the treatment of primary pulmonary hypertension (PPH) and pulmonary hypertension (PH) associated with the scleroderma spectrum of disease in New York Heart Association (NYHA) Class III-IV patients who do not respond adequately to conventional therapy.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Epoprostenol (Flolan™) therapy for the condition being addressed.

## FDA Approved Indications

Flolan is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

The New York Heart Association (NYHA) classification system - a functional and therapeutic classification for prescription of physical activity for cardiac patients is outlined in Table 1.

**Table 1 - New York Heart Association (NYHA) Classification**

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

### **FDA Recommended Dosing**

Chronic infusion of Flolan should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established and further increases in the infusion rate are not clinically warranted. If dose-limiting pharmacologic effects occur, then the infusion rate should be decreased to an appropriate chronic infusion rate whereby the pharmacologic effects of Flolan are tolerated.

### **Drug Availability**

Flolan for injection is supplied as a sterile freeze-dried powder in 17-mL flint glass vials with gray butyl rubber closures, individually packaged in a carton. Two 17-mL vials are available – either contain epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng).

### **General Background**

#### **Disease Overview**

Pulmonary Hypertension (also called PH, PPH, primary or secondary pulmonary hypertension or PAH for Pulmonary Arterial Hypertension) is a disease that causes the arteries of the lungs to constrict leading to right heart failure. 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 is 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 Doppler in the absence of secondary causes. It is of paramount importance to distinguish PAH from other types of 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**

<b>Group I</b>	<b>Pulmonary arterial hypertension (PAH)</b> <ul style="list-style-type: none"> <li>• <b>Idiopathic (IPAH)</b></li> <li>• <b>Familial (FPAH)</b></li> <li>• <b>Associated with (APAH)</b> <ul style="list-style-type: none"> <li>○ <b>Connective tissue disease</b></li> <li>○ <b>Congenital systemic-to-pulmonary shunts</b></li> <li>○ <b>Portal hypertension</b></li> <li>○ <b>HIV infection</b></li> <li>○ <b>Drugs and toxins</b></li> <li>○ <b>Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)</b></li> </ul> </li> <li>• <b>Associated with significant venous or capillary involvement</b> <ul style="list-style-type: none"> <li>○ <b>Pulmonary veno-occlusive disease (PVOD)</b></li> <li>○ <b>Pulmonary capillary haemangiomatosis (PCH)</b></li> </ul> </li> <li>• <b>Persistent pulmonary hypertension of the newborn (PPHN)</b></li> </ul>
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<b>Group II</b>	<b>Pulmonary hypertension associated with left heart diseases</b>
<b>Group III</b>	<b>Pulmonary hypertension associated with respiratory diseases and / or hypoxemia (including chronic obstructive pulmonary disease)</b>
<b>Group IV</b>	<b>Pulmonary hypertension due to chronic thrombotic and/or embolic disease</b>
<b>Group V</b>	<b>Miscellaneous group (eg. sarcoidosis, histiocytosis X and lymphangiomatosis)</b>

There are two injectable agents labeled for the treatment of PAH. The injectable agents include epoprostenol and treprostinil. Both agents are administered intravenously. Treprostinil can also be given subcutaneously, the preferred route of administration for this agent.

### **Guidelines**

Current treatment guidelines from the American College of Chest Physicians (2007) recommend treprostinil as a second-line agent in class II PAH, after sildenafil. The guidelines recommend epoprostenol and treprostinil as first-line injectable agents for class III PAH. Epoprostenol is also first-line in class IV PAH, followed by bosentan, iloprost, sildenafil, and treprostinil.

### **Clinical Efficacy**

Acute intravenous infusions of Flolan for up to 15 minutes in patients with secondary and primary pulmonary hypertension produce dose-related increases in cardiac index (CI) and stroke volume (SV) and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The effects of FLOLAN on mean pulmonary artery pressure (PAPm) were variable and minor.

Chronic continuous infusions of Flolan in patients with PPH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing Flolan plus conventional therapy to conventional therapy alone. Dosage of Flolan averaged 9.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described. Chronic hemodynamic effects were generally similar to acute effects. Increases in CI, SV, and arterial oxygen saturation and decreases in PAPm, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were observed in patients who received Flolan chronically compared to those who did not.

Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous Flolan plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with Flolan compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups showed no change in functional class, and 2/51 (4%) with Flolan and 13/48 (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with Flolan and 7 patients treated with conventional therapy alone. No statistical difference in survival over 12 weeks was observed in PH/SSD patients treated with Flolan as compared to those receiving conventional therapy alone. No controlled clinical trials with Flolan have been performed in patients with PH associated with other diseases.

Epoprostenol and treprostinil have similar efficacy when added to conventional therapy, although no comparative trials are available. Epoprostenol and treprostinil have been evaluated in a crossover study. Hemodynamics outcomes, including cardiac output, pulmonary artery pressure, and pulmonary vascular resistance, were similar between groups. Both agents improved hemodynamics when compared to placebo in a Cochrane systematic review. When used as monotherapy or adjunctive therapy, both agents significantly improved 6-minute walk distance from baseline. Results are similar in patients with idiopathic or secondary PAH. No controlled studies evaluate epoprostenol use in patients with class II PAH.

It is unknown whether concomitant therapy with more than one of the newer agents for PAH improves efficacy over monotherapy. In the only controlled trial, combination of epoprostenol and bosentan was not more effective in improving 6-minute walk distance than epoprostenol alone. Hemodynamics parameters were improved with the addition of nitric oxide or iloprost to epoprostenol monotherapy in short-term studies. Subcutaneous treprostinil has only been studied in combination with sildenafil. Exercise treadmill times and six-minute walk distance improved in evaluable patients. Results are similar in patients with idiopathic or secondary PAH.

Treatment with epoprostenol or treprostinil appears to increase survival rates nominally by 9-34% from that expected in patients with PAH, whether the specific agent is given alone or with other therapies as part of a treatment algorithm.

There are no published controlled trials which evaluate the clinical efficacy of epoprostenol and treprostinil solely in children. Many epoprostenol and treprostinil studies generally included pediatric patients, but results were not individually assessed for this patient population.

There are no controlled trials of these agents in pregnant women. Case reports or case series are available for only epoprostenol. In most reports, symptoms and functional class improved throughout pregnancy. All infants were well at delivery.

### Adverse Reactions

Diarrhea, flu-like symptoms, headache, jaw pain, flushing/vasodilation, nausea and vomiting, and nervousness are common adverse reactions related to epoprostenol. Injection site pain was reported in 9 to 12% of epoprostenol-treated patients. More blood stream infections are expected with epoprostenol administration. Higher mortality has been reported in NYHA Class III and IV patients with congestive heart failure secondary to severe left ventricular systolic dysfunction receiving epoprostenol plus conventional therapy than conventional therapy alone.

No clinically significant drug interactions have been reported with epoprostenol. An increase risk of bleeding may occur when administered with anticoagulant or antiplatelet agents. Additive blood pressure reductions may occur with epoprostenol when administered with antihypertensive drugs.

The usual adverse effects are associated with dose initiation, dose escalation and chronic administration. Side effects are hypotension, jaw pain, flushing/erythema, nausea and diarrhea. More long-term side effects include skin rash and chronic lower-extremity pain.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

HCPCS Codes	Description
J1325	Injection, epoprostenol, 0.5mg

ICD-9-CM Diagnosis Codes	Description
416.0	Primary pulmonary hypertension
416.8	Other chronic pulmonary heart diseases (secondary pulmonary hypertension)

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	10/15/2008	4096	Epoprostenol (Flolan™)
Great-West Healthcare	7/2007	P07.100.1	PAH

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.