



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.

Subject **Treprostinil (Remodulin®,
Tyvaso™)**

Effective Date 10/15/2010
Next Review Date.....10/15/2011
Coverage Policy Number 4039

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Hyperlink to Related Coverage Policies

[Epoprostenol \(Flolan™\)](#)

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 treprostinil (Remodulin®) as medically necessary for the treatment of individuals with New York Heart Association (NYHA) Class II-IV pulmonary arterial hypertension (PAH).

CIGNA covers treprostinil (Tyvaso™) as medically necessary for the treatment of individuals with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) and New York Heart Association (NYHA) Class III symptoms.

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 Treprostinil (Remodulin®, Tyvaso™) therapy for the condition being addressed.

FDA Approved Indications

Remodulin

Remodulin is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous

infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

In patients with PAH requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Tyvaso

Tyvaso is indicated to increase walk distance in patients with WHO Group I PAH and NYHA Class III symptoms. The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor).

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

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

FDA Recommended Dosing

Remodulin

Remodulin is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL.

Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

Tyvaso

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON-100/7 (an ultrasonic, pulsed-delivery device) and its accessories. Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart. Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated. Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose. If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose. The maximum recommended dosage is 9 breaths per treatment session, 4 times daily.

Drug Availability

Remodulin

Remodulin is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1 mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25degrees C (59 to 77 degrees F).

Tyvaso

Tyvaso inhalation system starter kit contains 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso inhalation system. Tyvaso inhalation system refill kit contains 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and accessories.

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 Doppler³ 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

Group I	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)

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. Tyvaso is a new, inhalation form of treprostinil.

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 Remodulin

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary PAH. PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital left to right shunts in 23%. The mean age was 45 (range 9 to 75 years). PH had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

The effect of Remodulin on 6-minute walk, the primary end point of the 12-week studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or Remodulin. Fourteen Remodulin and 8 placebo patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study. During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo. Thirteen of 14 patients in the Remodulin arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm ($p=0.0002$).

Tyvaso

Triumph I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with PAH (WHO Group I), nearly all with NYHA Class III symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/familial (56%), secondary to collagen vascular disease (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

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.

No trials have directly compared the effects of these agents on survival. However, 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

Remodulin

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment. Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea. These are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Tyvaso

In a 12-week placebo-controlled study of 235 patients with PAH (WHO Group I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included cough and throat irritation, headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

Coding/Billing Information

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

Covered when medically necessary:

HCPCS Codes	Description
J3285	Injection, treprostinil, 1 mg

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

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/15/2008	4039	Treprostinil (Remodulin®)
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.