Medication Policy Manual

Policy No: dru222

Topic: Remodulin®, treprostinil injectable

Date of Origin: September 1, 2010

Committee Approval Date: June 9, 2017

Next Review Date: April 2018

Effective Date: July 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Remodulin® (treprostinil injectable) is an injectable medication used in the treatment of pulmonary arterial hypertension.
Policy/Criteria

I. Most contracts require prior authorization approval of treprostinil injectable prior to coverage. Treprostinil injectable may be considered medically necessary for the treatment of pulmonary arterial hypertension (PAH) WHO Group 1 (See Appendix I).

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider treprostinil injectable to be a self-administered medication.

B. When prior authorization is approved, treprostinil injection may be authorized in quantities of up to 500 mg per claim. Authorization treprostinil injectable may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Treprostinil injectable is considered investigational when used for all other conditions, including but not limited to:

A. Pulmonary hypertension (PH) WHO Groups 2-5 (see Appendix II), including PH associated with:
   1. Left heart disease, including congestive heart failure (CHF)
   2. Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)
   3. Chronic thrombotic and/or embolic disease
   4. Sarcoidosis

Position Statement

- The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH. [1]

* Patients diagnosed with Group 1 pulmonary arterial hypertension (PAH) have generally irreversible disease and may require treatment with PAH-specific therapies.

* For patients with Groups 2-5, PH may be reversible. Therapy should be directed at treating the underlying cause. [1,2]

- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan, macitentan), PDE-5 inhibitors (sildenafil, tadalafil), and riociguat, a soluble guanylate cyclase (sGC) stimulator.

- The place in therapy of individual agents for PAH is not well defined and is typically symptom driven. Generally, a step-wise approach is used to manage patients. In early disease or with less severe symptoms, oral therapies may be used. As symptoms progress, inhaled or injectable therapies, such as epoprostenol injectable, iloprost inhaled and treprostinil injectable/inhaled, become necessary. [1]

© 2017 OmedaRx. All rights reserved.
dru222.7
Treprostinil injectable, given subcutaneously in doses up to 22.5 nanograms/kilogram/minute (ng/kg/min), has been shown to improve exercise tolerance in patients with pulmonary arterial hypertension (PAH). [3,4]

There are currently no trials of adequate design or of sufficient duration that demonstrate improved survival with treprostinil injectable in patients with PAH.

Treprostinil injectable, iloprost inhalation, treprostinil inhalation and treprostinil oral have been studied individually in the treatment of PAH. To date, there is no evidence that any one of these products is more effective than the other.

There are currently no trials of iloprost inhalation, treprostinil inhalation, treprostinil injectable, or treprostinil oral in patients with Groups 2-5 PH.

**Clinical Efficacy**

Iloprost inhalation, treprostinil inhalation, treprostinil injectable and treprostinil oral are used for the treatment pulmonary arterial hypertension (PAH) to improve exercise ability. [3,5-7] All were found to improve performance on the six-minute walk test relative to placebo. The six-minute walk test (6MWD) is a measure of exercise tolerance and measures the distance that is covered in a six-minute timeframe. Improvements in this test have been correlated to improve survival in PAH patients.

A single unreliable pivotal trial of 470 adults with PAH suggested that treprostinil injectable, given subcutaneously, may improve exercise capacity at 12-weeks based on the six-minute walk test compared to placebo. [4]

* The study was significantly flawed and is not able to be relied upon to make health care decisions. [4] Flaws included: lack of details regarding study design and incomplete reporting of results, including number of patients completing the study, therefore the validity of the trial is uncertain.

* The 6MWD is the standard used by the FDA for the approval of new drugs in the treatment of PAH, however the clinical relevance of less than a 10% improvement in 6MWD is not known.

* The trial was a short-term trial of only 12 weeks duration.

The safety and effectiveness of treprostinil injectable has not been established in pediatric patients. [3]

There is no reliable evidence that doses of treprostinil injectable exceeding 22.5 ng/kg/min provide any additional clinical benefit when used in the treatment of PAH. [4]

There is limited experience with doses exceeding 40 ng/kg/min. [3,8]

There are no well-designed trials that demonstrate additional benefit with treprostinil injectable when used in combination with other prostacyclins, riociguat (Adempas), any PDE5 inhibitors, or ETAs. [8,9]

ACCP guidelines for treatment of pulmonary arterial hypertension recommend the use of an ERA, PDE-5, or riociguat for treatment naïve PAH patients with WHO functional class (FC) II/III symptoms. Guidelines also recommend consideration of initial therapy with an injectable prostacyclin analog in WHO FC IV patients and select WHO FC III patients with rapid disease progression or poor prognostic markers. Inhaled prostacyclin may be added for patients with progressive symptoms despite one or two classes of oral
agents. ACCF/AHA guidelines recommend the use of iloprost inhalation in WHO Group 1 PAH (see Appendix I), based on systematic review of the literature.

Safety

- Safety data for treprostinil injectable is limited to adverse events described in the 12-week pivotal trial.

- The most frequent side effects reported (> 10%) were infusion site pain (85%), infusion site reaction (83%), headache (27%), diarrhea (25%), infusion system complications (23%), nausea (22%), rash (14%), jaw pain (13%), and vasodilation (11%). (The statistical significance of these adverse events versus placebo was not reported).

- Serious adverse events include severe infusion site pain (39%), severe infusion site reaction (38%), and bleeding. Thrombophlebitis (associated with peripheral intravenous infusion), thrombocytopenia, bone pain, generalized rashes, and cellulitis were identified as adverse reactions during post-approval use of treprostinil injection.

- Chronic intravenous infusion of treprostinil is delivered via an indwelling central venous catheter, with risk of infection and sepsis.

- The use of treprostinil injectable, iloprost inhalation and treprostinil inhalation is limited by their risk for potential side effects and need to be weighed against the risk/benefit ratio in using other therapeutic alternatives.

- Treprostinil injectable should be used only by clinicians experienced in the diagnosis and treatment of PAH.

- Clearance of treprostinil is reduced in patients with hepatic insufficiency, therefore these patients may be at increased risk of dose-dependent adverse events.

- Co-administration of treprostinil injectable with blood pressure lowering medications, such as diuretics, antihypertensive agents or other vasodilators, may increase the risk of systemic hypotension.

- Treprostinil inhibits platelet aggregation. Co-administration of treprostinil injectable with anticoagulants may further increase risk of bleeding.

- Co-administration of treprostinil injectable with of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) or inducer (e.g. rifampin) may alter treprostinil subcutaneous clearance and change clinical effectiveness or increase risk for adverse events.

Administration and Dosing

- The recommended dose of treprostinil injectable for the treatment of PAH is 1.25 ng/kg/min initially, with weekly dose titration of 1.25 to 2.5 ng/kg/min as tolerated. There is limited experience with doses exceeding 40 ng/kg/min.

- Lower initial dosing (0.625 ng/kg/min) and slow dose titration is recommended in patients with hepatic insufficiency, due to potential for higher systemic concentrations.
- Adjust dosage based on clinical response, including infusion site symptoms. Do not abruptly lower the dose or withdraw dosing. [3]

**Use of Treprostinil Injectable in Other Conditions**

- Guidelines do not support the use of treprostinil injectable for treatment of pulmonary hypertension (PH) in WHO Groups 2-5, including PH related to chronic left heart disease (WHO Group 2) or chronic hypoxic states (WHO Group 3). Instead, these patients require optimization of therapies targeting their underlying disease state. [1]
- No randomized, controlled trials have been published evaluating the use of treprostinil injectable in patients with sarcoidosis.

**Cross References**

| Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension, BlueCross BlueShield Association Medical Policy, 5.01.09, Issue 6.2016. |
| Adempas®, riociguat, Medication Policy Manual dru322 |
| bosentan-containing medications, Tracleer®, Medication Policy Manual dru218 |
| Letairis®, ambrisentan, Medication Policy Manual dru219 |
| Opsumit®, macitentan, Medication Policy Manual dru324 |
| Orenitram®, treprostinil oral tablets, Medication Policy Manual dru337 |
| Viagra®, Medication Policy Manual dru461 |
| tadalafil-containing medications, Cialis®, Adcirca®, Medication Policy Manual dru184 |
| Tyvaso®, treprostinil inhalation, Medication Policy Manual dru221 |
| Uptravi®, selexipag, Medication Policy Manual, dru446 |
| Ventavis®, iloprost inhalation, Medication Policy Manual dru220 |

**Codes**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>J3285</td>
<td>treprostinil injectable</td>
</tr>
</tbody>
</table>
References


Appendix I: Revised WHO Classification of Pulmonary Hypertension – Group 1 [1]

Group 1. Pulmonary arterial hypertension (PAH)
- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):
  - Connective tissue disorder (e.g. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, systemic sclerosis (formerly known as CREST syndrome))
  - Congenital systemic-to-pulmonary shunts (e.g. congenital heart disease (CHD), including atrial or ventricular septal defect, patent ductus arteriosus (PDA), patent foramen ovale (PFO), truncus arteriosus, Eisenmenger syndrome, tetralogy of Fallot, transposition of the great vessels)
  - Portal hypertension
  - HIV infection
  - Drugs and toxins (e.g. anorexic agents, cocaine, methamphetamine, L-tryptophan)
  - Other (thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (e.g. sickle cell anemia, thalassemia), chronic myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease (PVOD)
  - Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

* Diagnoses, include, but are not limited to these common diagnoses.

Appendix II: Investigational Indications for Sildenafil - Revised WHO Classification of PH – Groups 2-5 [1]

Group 2. Pulmonary hypertension with left heart disease
- Left-sided atrial or ventricular heart disease (systolic dysfunction, diastolic dysfunction)
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (e.g. idiopathic pulmonary fibrosis)
- Sleep disordered breathing (e.g. obstructive sleep apnea (OSA))
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5. Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)
Appendix III: Functional Status with Heart Failure


Class I: Patients with pulmonary hypertension (PH) but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by physical activity.

New York Heart Association (NYHA) Heart Failure Classification: [12]

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/9/2017</td>
<td>No changes to coverage criteria with this annual update.</td>
</tr>
<tr>
<td>6/10/2016</td>
<td>No changes</td>
</tr>
</tbody>
</table>

© 2017 OmedaRx. All rights reserved.