



**PRIOR AUTHORIZATION POLICY**

**POLICY:** Pulmonary Arterial Hypertension – Remodulin® (treprostinil injection for subcutaneous or intravenous use – United Therapeutics Corporation)

**TAC APPROVAL DATE:** 08/22/2018

**OVERVIEW**

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to diminish symptoms associated with exercise.<sup>1</sup> Studies establishing the effectiveness involved those with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). The risks and benefits of each agent should be considered carefully before transition.<sup>1</sup> Remodulin may be administered via continuous subcutaneous (SC) infusion or continuous intravenous infusion. However, chronic intravenous infusions of Remodulin given by an external infusion pump with an indwelling venous catheter are associated with potential blood stream infections and sepsis, which can be fatal. Continuous SC infusion is the preferred route of administration. In those with PAH requiring transition from epoprostenol injection, Remodulin is indicated to diminish the rate of clinical deterioration. Several trials have shown benefits of Remodulin therapy.<sup>1-8</sup>

Pulmonary hypertension can be classified into five different groups. Remodulin is indicated in Group 1 PAH.<sup>1</sup> The five major category of pulmonary hypertension are cited in Table 1.<sup>17</sup>

**Table 1. Updated Classification of Pulmonary Hypertension.<sup>17</sup>**

<p><b>Group 1: Pulmonary Arterial Hypertension</b></p> <ul style="list-style-type: none"> <li>Idiopathic</li> <li>Heritable <ul style="list-style-type: none"> <li>BMPR2</li> <li>ALK-1, ENG, SMAD9, CAV1, KCNK3</li> <li>Unknown</li> </ul> </li> <li>Drug and toxin-induced</li> <li>Associated with <ul style="list-style-type: none"> <li>Connective tissue disease</li> <li>Human immunodeficiency virus infection</li> <li>Portal hypertension</li> <li>Congenital heart diseases</li> <li>Schistosomiasis</li> </ul> </li> <li>Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</li> <li>Persistent pulmonary hypertension of the newborn</li> </ul>
<p><b>Group 2: Pulmonary Hypertension Due to Left Heart Disease</b></p> <ul style="list-style-type: none"> <li>Left ventricular systolic dysfunction</li> <li>Left ventricular diastolic dysfunction</li> <li>Valvular disease</li> <li>Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</li> </ul>

**Table 1 (continued). Updated Classification of Pulmonary Hypertension.<sup>17</sup>**

<p><b>Group 3: Pulmonary Hypertension Due to Lung Diseases and/or Hypoxemia</b>  Chronic obstructive pulmonary disease  Interstitial lung disease  Other pulmonary diseases with mixed restrictive and obstructive pattern  Sleep-disordered breathing  Alveolar hypoventilation disorders  Chronic exposure to high altitude  Developmental lung diseases</p>
<p><b>Group 4: Chronic Thromboembolic Pulmonary Hypertension</b></p>
<p><b>Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms</b>  Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy  Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis  Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders  Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.</p>

BMP2 – Bone morphogenetic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; Smad 9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

The WHO classification of functional status, which is an adaptation of the NYHA system, is in Table 2.<sup>10</sup> This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy.

**Table 2. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.<sup>10</sup>**

Class	Description
I	Patients in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

WHO – World Health Organization.

### Clinical Efficacy

Remodulin, given by continuous SC infusion, was studied in two 12-week, multicenter, randomized, double-blind, placebo-controlled trials in 470 patients with NYHA Class II (11%), Class III (81%), or Class IV (7%) PAH (mean disease duration: 3.8 years).<sup>1-2</sup> PAH was idiopathic/heritable in 58% of patients, associated with connective tissue diseases in 19% of patients, and the result of congenital systemic-to-pulmonary shunts in 23% of patients. Background therapy used in these studies included anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen, but not an endothelin receptor antagonist (ERA) or epoprostenol injection. The primary endpoint was change in the 6-minute walk distance. At Week 12, the Remodulin SC infusion dose averaged 9.3 ng/kg/min. The effect of Remodulin on 6-minute walk distance was small and did not achieve statistical significance. For the combined population, the median change from baseline was 10 meters and 0 meters on Remodulin and placebo, respectively (baseline 345 meters). The Borg dyspnea score (subjective assessment of shortness of breath during the 6-minute walk distance) was significantly improved by treatment with Remodulin. In addition, Remodulin given by continuous SC infusion also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, although difficult to assess in the context of incomplete blinding to treatment assignment due to infusion site symptoms.

Remodulin has also been studied in patients transitioning from epoprostenol injection.<sup>1</sup> In an 8-week, multicenter, randomized, double-blind, placebo-controlled study patients on stable doses of epoprostenol injection were randomly withdrawn from epoprostenol injection therapy and given placebo or Remodulin.

Fourteen Remodulin patients and 8 patients given placebo completed the study. The primary endpoint was the time to clinical deterioration, defined as either an increase in the epoprostenol injection dose, hospitalization due to PAH, or death. During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from epoprostenol injection therapy compared with placebo with 92% and 12% not reporting a clinical deterioration event for Remodulin and placebo, respectively (P = 0.000228). Thirteen out of 14 patients given Remodulin were able to transition from epoprostenol injection to Remodulin successfully, compared with 1 of 8 patients in the placebo arm (P = 0.0002).

Remodulin has been studied in open-label, uncontrolled trials.<sup>5,8</sup> One trial reported a significant improvement in the six-minute walk distance in sixteen NYHA Functional Class III or IV patients with PAH treated with Remodulin monotherapy.<sup>8</sup> In a similar 12-week, open-label trial, 31 patients with NYHA Functional Class II and III patients with PAH were transitioned from epoprostenol injection to intravenous Remodulin.<sup>5</sup> Twenty-seven patients completed the transition while four patients were transitioned back to epoprostenol injection. The six-minute walk distance was maintained among the patients who completed the transition.

### **Guidelines**

In 2004, the American College of Chest Physicians (ACCP) developed evidence-based clinical practice guidelines regarding the screening, early detection, and diagnosis of PAH.<sup>9</sup> In patients with suspected pulmonary hypertension, right heart catheterization is required to confirm the presence of pulmonary hypertension, establish the specific diagnosis, and determine disease severity (grade A recommendation). In patients with suspected pulmonary hypertension, right heart catheterization is required to guide therapy (grade B recommendation).<sup>10</sup> The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.<sup>11</sup>

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.<sup>9</sup> The guidelines state that the diagnosis of PAH requires confirmation with a complete right heart catheterization. The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units.

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Remodulin. Because of the specialized skills required for evaluation and diagnosis of patients treated with Remodulin as well as the monitoring required for adverse events and long-term efficacy, approval requires Remodulin to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

**Documentation:** In the *Pulmonary Arterial Hypertension – Remodulin Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Remodulin Prior Authorization Policy* is considered to be met.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Remodulin is recommended in those who meet the following criteria:

### FDA-Approved Indications

#### 1. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].

Approve for the duration noted if the patient meets ONE of the following (A or B):

**A) Initial Therapy.** Approve for 3 years if the patient meets all of the following criteria (i, ii, iii, iv, and v):

- i.** The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- iii.** The patient meets the following criteria (a and b):
  - a)** The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
  - b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- iv.** The patient meets ONE of the following criteria (a or b):
  - a)** The patient is in Functional Class III or IV; OR
  - b)** The patient is in Functional Class II and meets ONE of the following criteria (1 or 2):
    - (1)** The patient has tried or is currently receiving one oral agent for PAH (e.g., Tracleer<sup>®</sup> [bosentan tablets], Letairis<sup>®</sup> [ambrisentan tablets], Opsumit<sup>®</sup> [macitentan tablets], Adempas<sup>®</sup> [riociguat tablets], Revatio<sup>®</sup> [sildenafil tablets {generic} and oral suspension], Adcirca<sup>®</sup> [tadalafil tablets {generic}], Orenitram<sup>™</sup> [treprostinil extended-release tablets] or Uptravi<sup>®</sup> [selexipag tablets]); OR
    - (2)** The patient has tried one inhaled or parenteral prostacyclin product for PAH (e.g., Ventavis<sup>®</sup> [iloprost inhalation solution], Tyvaso<sup>®</sup> [treprostinil inhalation solution], epoprostenol injection); AND
- v.** Patients with idiopathic PAH must meet ONE of the following criteria (a, b, c, d, or e):
  - a)** The patient has had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy (e.g., amlodipine, nifedipine extended-release tablets); OR
  - b)** The patient did not have an acute response to vasodilator testing; OR
  - c)** The patient cannot undergo a vasodilator test; OR
  - d)** The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
  - e)** The patient has tried one CCB (e.g., amlodipine, nifedipine extended-release tablets); OR

**B) Patients Currently Receiving Remodulin.** Approve for the duration noted below if the patient meets the following criteria (i or ii):

- i.** Approve for 3 years if the patient meets ALL of the following conditions (a, b, and c):
  - a)** The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

- b) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist;  
AND
- c) The patient meets the following criteria (1 and 2):
  - (1) The patient has had a right heart catheterization; AND
  - (2) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; OR
- ii. Approve a short-term supply of Remodulin for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. Note: a 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of Remodulin therapy may have severe adverse consequences.

Remodulin is indicated for the treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise.<sup>1</sup> Studies establishing effectiveness included patients with NYHA Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).<sup>1</sup> The World Symposium on Pulmonary Hypertension (WSPH) updated treatment algorithm of PAH recommend SC Remodulin and intravenous Remodulin in patients WHO Functional Class III or Class IV.<sup>16</sup> Patients in Functional Class II should be treated with an oral agent for PAH (e.g., Tracleer, Opsumit, Letairis, Adempas, sildenafil, Adcirca). ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH disease severity.<sup>10</sup> An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, the ATS, and the Pulmonary Hypertension Association, note all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to the initiation of therapy.<sup>9</sup> The current hemodynamic definition of PAH is a mPAP greater than 25 mmHg; a PCWP, a LAP, or a LVEDP less than or equal to 15 mmHg; and a PVR greater than 3 Wood units. Acute vasodilator testing should be done in all patients with idiopathic PAH who might be considered potential candidates for long-term CCB therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP to at least 10 mm Hg or an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output.<sup>9</sup>

### Other Uses with Supportive Evidence

2. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve for 3 years if prescribed by, or in consultation with, a pulmonologist or a cardiologist.

Surgical pulmonary thromboendarterectomy (PTE) is the treatment of choice in symptomatic CTEPH.<sup>12,18-19</sup> A prospective, uncontrolled observational cohort study analyzed the efficacy of long-term SC Remodulin in a difficult subset of inoperable CTEPH patients with severe symptoms (n = 25).<sup>13</sup> Overall survival rates at 1, 2, 3 and 5 years were 80%, 80%, 80% and 53%, respectively, compared with untreated patients showing survival rates of 67%, 43%, 37%, and 16%, respectively (P = 0.02).<sup>13</sup> Other data are available regarding use of Remodulin in CTEPH.<sup>14</sup> The 4<sup>th</sup> World Symposium on Pulmonary Hypertension published a paper that focused on non-PAH forms of pulmonary hypertension in 2009.<sup>12</sup> This paper notes in those with inoperable CTEPH, medical therapy may be appropriate, and patients should be considered for enrollment in clinical trials. Preliminary data suggest that medications currently approved for PAH may have beneficial effects in

patients with CTEPH, but as long as there are no robust data from randomized controlled trials, the decision of whether or not to treat CTEPH patients with these medications should be restricted to centers experienced in the management of the disease. If surgery is not possible, only limited options are available for patients with CTEPH.<sup>12</sup> The guidelines have not been updated since the approval of Adempas for CTEPH.<sup>20</sup> In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Remodulin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Chronic Obstructive Pulmonary Disease (COPD) in a Patient without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.<sup>15</sup>
- 2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.** Criteria will be updated as new published data are available.

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### HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	For patients with PAH (WHO Group 1), for patients in Functional Class II, Uptravi was added as a medication option that counts towards the requirement to try one agent. Also, the phrase “women of childbearing potential” was changed to “patient of childbearing potential” in reference to exceptions to the requirement that one oral agent be tried first.	08/10/2016
Annual revision	No criteria changes.	08/30/2017
Annual revision	For initial review, documentation is required for the right heart catheterization and the result confirm the diagnosis of WHO Group 1 PAH. The specific values required from the heart catheterization test were removed. For patients currently receiving Remodulin a right heart catheterization is required and the results should confirm the diagnosis of WHO Group 1 PAH, but documentation is not required, nor are the specific values required. For patients in Functional Class II, the exceptions to use of other medications was removed as these can be handled on a case by case basis. Viagra and Cialis were removed from the listing of medications for WHO Group 1 PAH as Revatio and Adcirca are available generically. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met. Criteria that provided a 14-day approval for patients currently receiving Remodulin for any indication were removed.	08/22/2018

TAC – Therapeutic Assessment Committee; \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; PAH – Pulmonary arterial hypertension; WHO – World Health Organization; CCB – Calcium channel blocker.