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**Medication Policy Manual**

**Policy No:** dru322

**Topic:** Adempas®, riociguat

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**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**

Adempas (riociguat) is an oral medication used in the treatment of pulmonary arterial hypertension (PAH) as well as pulmonary hypertension due to chronic lung clots (CTEPH).

## Policy/Criteria

- I. Most contracts require prior authorization approval of riociguat prior to coverage. Riociguat may be considered medically necessary for treatment of:
- A. **Pulmonary arterial hypertension (PAH)** when criteria 1 and 2 below are met:
    - 1. There is a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH) (See Appendix I).
  - AND
  - 2. Sildenafil has been ineffective, not tolerated, or contraindicated.
- OR
- B. **Pulmonary hypertension (PH) associated with chronic thrombotic and/or embolic disease (CTEPH)** [WHO Group 4], (see Appendix II), that is inoperable or with residual PH after pulmonary thromboendarterectomy (PTE).
- II. Administration, Quantity Limitations, and Authorization Period
- A. Regence Pharmacy Services considers riociguat to be a self-administered medication.
  - B. When prior authorization is approved, riociguat may be authorized in quantities of 90 tablets per month.
  - C. Authorization of riociguat may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
- III. Riociguat is considered investigational when used for all other conditions, including but not limited to:
- A. Use in combination with any phosphodiesterase inhibitor, including sildenafil (generic Revatio), tadalafil (Adcirca), dipyridamole, or theophylline.
  - B. All other types of pulmonary hypertension (PH) (see Appendix II), including PH associated with:
    - 1. Left heart disease, including congestive heart failure (CHF) (WHO Group 2)
    - 2. Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) (WHO Group 3)
    - 3. Miscellaneous causes, such as sarcoidosis (WHO Group 5)
  - C. Raynaud's phenomenon, with or without digital ulcers.

## Position Statement

- The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH. <sup>[1]</sup>
  - \* 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, such as clot removal for PH due to chronic thromboemboli (CTEPH) with pulmonary thromboendarterectomy (PTE). <sup>[1,2]</sup>
- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (PGEs) (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan), PDE-5 inhibitors (PDE5s) (sildenafil, tadalafil), and the soluble guanylate cyclase stimulator riociguat.
- 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. <sup>[1]</sup>
- There is insufficient evidence to establish any one oral therapy for PAH is clearly superior to another. Generic sildenafil is the lowest-cost oral medication for PAH and a treatment option for most treatment-naïve PAH patients.
- For pulmonary hypertension due to CTEPH, surgical clot removal with pulmonary thromboendarterectomy (PTE) is the treatment of choice. PAH medication therapies may be considered for patients unable to have surgery or with residual PH; however, the evidence for efficacy is limited. All CTEPH patients should receive along with lifelong anticoagulation. <sup>[3]</sup>
- Riociguat has been FDA-approved for and may be a treatment option for inoperable or recurrent CTEPH and PAH.
- In patients with PAH and CTEPH (inoperable or recurrent), riociguat improved exercise tolerance (six minute walking distance, 6MWD) as well as symptoms (functional class). Riociguat also delayed time to clinical worsening in patients with PAH. <sup>[4]</sup>
- There are currently no trials of adequate design or of sufficient duration that demonstrate improved survival with riociguat in patients with PAH or CTEPH.
- There are no head-to-head comparative studies of riociguat with other therapies for PH.
- Although the pivotal PAH trial allowed use of riociguat in combination with bosentan or inhaled prostanoids (PGEs), use of riociguat with any phosphodiesterase inhibitor (e.g. sildenafil, tadalafil, dipyridamole, theophylline) is contraindicated due to excessive hypotension in combination.

- There are currently no trials of riociguat in patients with other types of PH (Groups 2, 3 or 5). Choosing Wisely®, an evidence-based initiative to promote wise use of medical resources, states that medications for PAH (e.g. PGEs, PDE5s, and ETAs) should not be used in patients with pulmonary hypertension due left heart disease or hypoxemic lung diseases (Groups 2 and 3), due to a lack of established benefit. In addition, medications for PAH may be harmful in some situations and raises the overall cost of care. [5]
- Riociguat is being studied in Raynaud's for effects on digital blood flow.
- Use of riociguat in combination with any phosphodiesterase inhibitor, including sildenafil, tadalafil, dipyridamole, or theophylline, is contraindicated, due to significant risk of hypotension.
- Riociguat may be covered at the doses at which it has been shown to be effective. The usual dose is 1 to 2.5 mg orally three times a day, titrated generally every two weeks, as tolerated.

### *Clinical Efficacy*

- Riociguat is used for the treatment for both CTEPH and pulmonary arterial hypertension (PAH) to improve exercise ability, symptoms and time to clinical worsening. [4] It was found to improve performance on the 6-minute walk test, as well as symptoms (functional class) relative to placebo. The six-minute walk test (6MWD) is a measure of exercise tolerance and measures the distance that is covered in a 6-minute timeframe. Improvements in this test have been correlated to improved survival in PAH patients. WHO functional class is a measure of activity level and correlated with disease severity and outcomes, but can be prone to reporting bias.
- The efficacy and safety of riociguat was evaluated in two published randomized, double-blind, placebo-controlled trials in both CTEPH (n =261) and PAH patients (n = 443). The primary endpoint for both trials was improvement in exercise capacity, as measured by six minute walking distance (6MWD), a validated surrogate marker for PH treatment response. [6,7]
  - o CTEPH: Riociguat was superior to placebo for improvement in 6MWD at 16 weeks (+ 46 meters (m), placebo-adjusted; mean baseline 347 m). In addition, symptoms (functional class) improved more frequently (33% vs. 15% placebo).
  - o PAH: Riociguat 2.5 mg three times daily was superior to placebo for improvement in 6MWD at 12 weeks (+ 36 m, placebo-adjusted; mean baseline 363 m). In addition, symptoms improved more frequently (21% vs. 14% placebo) and time to clinical worsening delayed. Of note, half of the patients continued on previously established PAH medications (44% bosentan, 6% non-intravenous PGE).
- The safety and effectiveness of riociguat has not been established in pediatrics. [4]
- There is no clinical trial evidence that doses of riociguat exceeding 2.5 mg three times a day provide any additional clinical benefit when used in the treatment of CTEPH or PAH.
- There are no trials of riociguat for CTEPH in combination with any other PAH medications.

- Although some patients received riociguat in combination with ETAs or inhaled PGEs during the PAH pivotal trial, there are no well-designed trials that demonstrate additional clinical benefit when riociguat is used in combination with other PAH medications, such as epoprostenol IV or injectable treprostinil.
- ACCP guidelines for treatment of pulmonary arterial hypertension recommend the use of an ETA, 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. [8] ACCF/AHA guidelines for treatment of both pulmonary hypertension and pulmonary embolism do not include riociguat, as it was not available at the time the guidelines were published. [1,3]

#### *Safety* [4]

- Safety data for riociguat is limited to adverse events described in two pivotal trials, of 12 weeks and extension trials out to 663 days. Long-term open-label extension trial interim analyses reported safety data at one year.
- Riociguat has a safety profile similar to other pulmonary vasodilators, such as PDE5s and PGEs. The most common adverse effects (AEs) ( $\geq 3\%$  more than placebo) include headache, dizziness, dyspepsia/ gastritis, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation.
- Serious adverse effects include bleeding and worsening of pulmonary veno-occlusive disease (PVOD), as well as hypotension, an adverse effect common to all PH medications. Combination with other vasodilators potentiates hypotension. Bleeding, including hemoptysis, was reported in 1-3% of patients in the long-term extension trials or riociguat. However, many of the patients were on concomitant anticoagulants for CTEPH; therefore, the absolute risk of bleeding with riociguat is unknown. [9,10]
- Patients with a systolic blood pressure less than 95 mm Hg were excluded from clinical trials; therefore, the safety of riociguat in hypotensive patients is unknown.
- Coadministration of phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) with riociguat is contraindicated, due to additive hypotension leading to a high rate of discontinuation. In addition, there was one death possibly related to the combination of riociguat and sildenafil.
- Like other oral PH medications, there are a number of significant drug interactions with riociguat. Strong inhibitors of cytochrome (CYP) and P-gp/BCRP metabolism pathways (e.g. ketoconazole, ritonavir) can increase levels, whereas smoking and antacids decreases serum levels. Dose adjustment is recommended.
- Riociguat is only available through a Risk Evaluation and Mitigation Strategy (REMs) program, to ensure riociguat is not used in pregnant women, due to the risk of fetal harm.

### *Administration and Dosing* <sup>[4]</sup>

- The recommended dose of riociguat for the treatment of CTEPH or PAH is 1 to 2.5 mg three times a day daily.
- It is unknown if there is an additional benefit above the recommended dose.

### *Use of Riociguat in Other Conditions*

Other potential uses of riociguat include the treatment of Raynaud's phenomenon and other types of pulmonary hypertension.

- No randomized, controlled trials have been published evaluating the use of riociguat in any other indications, aside from CTEPH and PAH.
- Trials of riociguat in Raynaud's phenomenon, for improvement of digital blood flow, are ongoing. <sup>[11]</sup>
- Although riociguat was not included in treatment guidelines as a newly approved medication, guidelines do not support the use of other PAH medication 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. <sup>[1]</sup>

<b>Cross References</b>
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bosentan-containing medications, Tracleer <sup>®</sup> , Medication Policy Manual, dru218
Letairis <sup>®</sup> , ambrisentan, Medication Policy Manual, dru219
Opsumit, macitentan, Medication Policy Manual, dru324
Orenitram, treprostinil oral tablets, Medication Policy Manual, dru337
Remodulin <sup>®</sup> , treprostinil injectable, Medication Policy Manual, dru222
Viagra <sup>®</sup> , Medication Policy Manual, dru461
tadalafil-containing medications, Cialis <sup>®</sup> , Adcirca <sup>®</sup> , Medication Policy Manual, dru184
Tyvaso <sup>®</sup> , treprostinil inhalation, Medication Policy Manual, dru221
Uptravi <sup>®</sup> , selexipag, Medication Policy Manual, dru446
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## **Appendix I: Revised World Health Organization (WHO) Classification of pulmonary hypertension (PH) – Group 1 <sup>[1]</sup>**

### **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 <sup>[1]</sup>**

### **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**

#### World Health Organization (WHO) functional assessment classification: <sup>[12]</sup>

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: <sup>[13]</sup>

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*

<b>Revision Date</b>	<b>Revision Summary</b>
6/9/2017	No changes to coverage criteria with this annual update.
6/10/2016	No changes