# Clinical Policy: Riociguat (Adempas)

Reference Number: PA.CP.PHAR.195
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications
Revision Log

**Description**
Riociguat (Adempas®) is a soluble guanylate cyclase stimulator.

**FDA Approved Indication(s)**
Adempas is indicated:

- For the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (World Health Organization [WHO] Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class;
- For the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class, and to delay clinical worsening;
  - Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

**Policy/Criteria**
It is the policy of health plans affiliated with Pennsylvania Health and Wellness Corporation® that Adempas is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Pulmonary Hypertension** (must meet all):

1. Diagnosis of PAH or CTEPH;
2. Prescribed by or in consultation with a cardiologist or pulmonologist;
3. Member meets one of the following (a or b):
   a. For PAH: Failure of a calcium channel blocker, unless member meets one of the following (i, ii, or iii):
      i. Inadequate response or contraindication to acute vasodilator testing;
      ii. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
      iii. Members already taking and stabilized on riociguat will not be required to change therapy;
   b. For CTEPH: Disease is inoperable or persistent (i.e., suboptimal surgical outcome);
4. Dose does not exceed 7.5 mg per day (*patients who smoke may require higher doses*).

**Approval duration: 6 months**

**B. Other diagnoses/indications:** Refer to PA.CP.PMN.53

**II. Continued Approval**

**A. Pulmonary Hypertension** (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies ;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 7.5 mg per day *(patients who smoke may require higher doses).*

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

**Background**

*Description/Mechanism of Action:*

Adempas (riociguat) is a tablet for oral administration. Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of nitric oxide and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat has a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO. Riociguat stimulates the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation. The active metabolite (M1) of riociguat is 1/3 to 1/10 as potent as riociguat.

**III. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

CTEPH: chronic thromboembolic pulmonary hypertension
FC: functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
WHO: World Health Organization

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| nifedipine (Adalat® CC, Afeditab® CR, Procardia®, Procardia XL®) | 60 mg PO QD; may increase to 120 to 240 mg/day | 240 mg/day |
| diltiazem (Dilacor XR®, Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA) | 720 to 960 mg PO QD | 960 mg/day |
| amlodipine (Norvasc®) | 20 to 30 mg PO QD | 30 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Pregnancy
  - Nitrates and nitric oxide donors
  - Phosphodiesterase inhibitors
  - Pulmonary hypertension associated with idiopathic interstitial pneumonitis
- Boxed warning(s): embryo-fetal toxicity

*Appendix D: Pulmonary Hypertension: WHO Classification*

- Group 1: PAH (pulmonary arterial hypertension)
- Group 2: PH due to left heart disease
- Group 3: PH due to lung disease and/or hypoxemia
- Group 4: CTEPH (chronic thromboembolic pulmonary hypertension)
- Group 5: PH due to unclear multifactorial mechanisms

*Appendix E: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)*

| Treatment Approach* | FC | Status at Rest | Tolerance of Physical Activity (PA) | PA Limitations | Heart Failure |
|---|---|---|---|---|---|
| Monitoring for progression of PH and treatment of co-existing conditions | I | Comfortable at rest | No limitation | Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope. | |
| Advanced treatment of PH with PH-targeted therapy | II | Comfortable at rest | Slight limitation | Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope. | |

| Treatment Approach* | FC | Status at Rest | Tolerance of Physical Activity (PA) | PA Limitations | Heart Failure |
|---|---|---|---|---|---|
| - *see Appendix F*** | III | Comfortable at rest | Marked limitation | Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope. | |
| | IV | Dyspnea or fatigue may be present at rest | Inability to carry out any PA without symptoms | Discomfort is increased by any PA. | Signs of right heart failure |

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.

*Appendix F: Pulmonary Hypertension: Targeted Therapies*

| Mechanism of Action | Drug Class | Drug Subclass | Drug | Brand/Generic Formulations |
|---|---|---|---|---|
| Reduction of pulmonary arterial pressure through vasodilation | Prostacyclin* pathway agonist<br><br>**Member of the prostanoid class of fatty acid derivatives.* | Prostacyclin | Epoprostenol | Veletri (IV)<br>Flolan (IV)<br>Flolan generic (IV) |
| | | Synthetic prostacyclin analog | Treprostinil | Orenitram (oral tablet)<br>Remodulin (IV)<br>Tyvaso (inhalation) |
| | | | Iloprost | Ventavis (inhalation) |
| | | Non-prostanoid prostacyclin receptor (IP receptor) agonist | Selexipag | Uptravi (oral tablet) |
| | Endothelin receptor antagonist (ETRA) | Selective receptor antagonist | Ambrisentan | Letairis (oral tablet) |
| | | Nonselective dual action receptor antagonist | Bosentan | Tracleer (oral tablet) |
| | | | Macitentan | Opsumit (oral tablet) |
| | Nitric oxide-cyclic guanosine monophosphate enhancer | Phosphodiesterase type 5 (PDE5) inhibitor | Sildenafil | Revatio (IV, oral tablet, oral suspension) |
| | | | Tadalafil | Adcirca (oral tablet) |
| | | Guanylate cyclase stimulant (sGC) | Riociguat | Adempas (oral tablet) |

## IV. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| Pulmonary arterial hypertension | 1 mg PO TID, increased by 0.5 mg every 2 weeks as tolerated to 2.5 mg TID | 7.5 mg/day |
| CTEPH | | |

## V. Product Availability

Tablets: 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg

## Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| N/A | |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|---|---|---|
| Removed WHO/NYHA classifications from initial criteria since specialist is involved in care. References reviewed and updated. | 02/18 | |
| 1Q 2019 annual review: references reviewed and updated. | 01/19 | |

## References

1. Adempas Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; January 2018. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Adempas_PI.pdf. Accessed November 7, 2018.
2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association - developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53(17): 1573-1619.
3. Taichman D, Ornelas J, Chung L, et. al. CHEST guideline and expert panel report: Pharmacologic therapy for pulmonary arterial hypertension in adults. Chest. 2014; 146 (2): 449-475.
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5. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013; 62(25): Suppl D92-99.

6. Galiè N, Humbert M, Vachiary JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of Pulmonary Hypertension. European Heart Journal. Doi:10.1093/eurheartj/ehv317.