Clinical Policy Title:	riociguat
Policy Number:	RxA.007
Drug(s) Applied:	Adempas®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

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

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%).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
riociguat (Adempas®)	Pulmonary arterial hypertension	1 mg PO three times daily, increased by 0.5 mg every 2 weeks as tolerated to 2.5 mg three times daily.	7.5 mg/day
	CTEPH		

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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:
    i. For PAH: Failure of a calcium channel blocker (see Appendix B), unless member meets one of the following (a or b):
        a. Inadequate response or contraindication to acute vasoreactivity testing;
        b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
    i. 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Pulmonary Hypertension (must meet all):

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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 Organisation

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
nifedipine (Adalat® CC, Procardia®, Procardia XL®)	60 mg PO Once daily; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)	720 to 960 mg PO Once daily	960 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
amlodipine (Norvasc®)	20 to 30 mg PO Once daily	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: General Information

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.	
- 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 *Member of the prostanoid class of fatty acid derivatives.	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) 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)

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 February 19, 2021.
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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. Accessed February 19, 2021.
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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
2Q2020 P&T Review; No updates, references reviewed and updated	4/2020	05/20/2020
Policy was reviewed: 1. Policy title table was updated. 2. Continued therapy approval criteria II.A.1 and II.B.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 3. Approval duration section was updated to include commercial plans for initial and continued therapy criteria. 4. Appendix B standard verbiage was updated to “Below are suggested therapeutic alternatives based on clinical guidance...”. Table also updated to remove discontinued brands	02/19/2021	03/09/2021

Afeditab® CR, Dilacor XR. 5. Dosing frequency sig codes were expanded. 6. References were updated.		