Drug Monograph

Drug/Drug Class:	**Adempas™ (riociguat) Tablets/ guanylate cyclase stimulator**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg tablet of Adempas contains 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg respectively of riociguat. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981
Summary of Findings:	Adempas is the first agent in a new class of medications called soluble guanylate cyclase stimulators and the first agent to be approved for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) following surgical treatment or for inoperable disease. It is also approved for the treatment of pulmonary arterial hypertension (PAH) in adults to improve exercise capacity and delay clinical worsening.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Patients suffering from CTEPH or PAH have greatly reduced vascular resistance and exercise capacity leading to decreased quality of life and, if left untreated, signs of heart failure and death.

Dosage Form(s)[1]

Each 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg Adempas tablet contains 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg respectively of riociguat.

Manufacturer

Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981

Indication(s)[1]

Adempas is FDA approved for the treatment of PAH (WHO Group 1) in adults to improve exercise capacity and delay clinical worsening, and for the treatment of persistent/recurrent CTEPH (WHO Group 4) in adults following surgical treatment or for inoperable disease, to improve exercise capacity and WHO functional class.

Clinical Efficacy[1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Adempas stimulates soluble guanylate cyclase (sGC), which is the receptor for nitric oxide and an enzyme in the cardiopulmonary system. When nitric oxide binds to sGC, it catalyzes the synthesis of cyclic guanosine monophosphate (cGMP), which regulates processes that influence vascular tone, proliferation, fibrosis, and inflammation. Adempas sensitizes sGC to endogenous nitric oxide, directly stimulates sGC at a different binding site independent of nitric oxide, and increases generation of cGMP and subsequent vasodilation.

	ADEMPAS
Protein binding	95%
Volume of distribution	30 L
Metabolism	Liver, via CYP1A1 to active metabolite, also via CYP3A, CYP2C8, and CYP2J2.
Excretion	Urine (40%)
Half-life	Feces (53%)

Efficacy of Adempas was established in two phase 3, randomized, double-blind, placebo-controlled trials. The 16-week Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase - Stimulator Trial 1 (CHEST-1) was conducted in patients with CTEPH and the 12-week Pulmonary Arterial Hypertension Soluble Guanylate Cyclase - Stimulator Trial 1 (PATENT-1) was conducted in patients with symptomatic PAH. In each trial, Adempas improved exercise capacity and pulmonary vascular resistance.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION - Study 1

STUDY DESIGN	Randomized, multicenter, double-blind, placebo-controlled, phase 3 study (n=261).
INCLUSION CRITERIA	Adult patients with inoperable CTEPH or recurrent or persistent pulmonary hypertension following pulmonary endarterectomy.
EXCLUSION CRITERIA	Patients who received an endothelin-receptor antagonist, prostacyclin analogue, phosphodiesterase type 5 inhibitor, or nitric oxide donor within the prior 3 months.
TREATMENT REGIMEN	Participants (mean age, 59 +/- 14 years) were randomized to receive 16 weeks of Adempas (n=173) or placebo (n=88). Adempas was initiated at 1 mg 3 times/day and titrated every 2 weeks up to 2.5 mg 3 times/day, based on patient systolic arterial pressure and signs or symptoms of hypotension. The maximum dose of 2.5 mg 3 times/day was achieved in 77% of patients, while 12%, 6%, 4%, and 1% of patients were titrated to Adempas doses of 2 mg, 1.5 mg, 1 mg, and 0.5 mg 3 times/day, respectively.
RESULTS	At baseline, most patients were at WHO functional class II (31%) or class III (64%), with a mean baseline 6MWD of 347 +/- 80 meters among all patients. The change in 6MWD from baseline to 16 weeks (primary endpoint) increased by a mean of 39 m in the Adempas arm compared with a mean decrease of 6 m in the placebo arm (mean difference, 46 m; 95% CI, 25 to 67 m; $p < 0.001$). Compared with the placebo arm, the Adempas arm also demonstrated a significant decrease in pulmonary vascular resistance (mean difference, -246 dyn x sec/cm(5); 95% CI, -303 to -190 dyn x sec/cm(5); $p < 0.001$) and in N-terminal pro-brain natriuretic peptide (NT-proBNP) level (mean difference, -444 picograms (pg)/mL; 95% CI, -843 to -45 pg/mL; $p < 0.001$) from baseline to week 16. Additionally, the proportion of patients with an improved WHO functional class from baseline to week 16 was 33% in the Adempas group compared with 15% in the placebo group (p=0.003).
SAFETY	Serious drug-related adverse events in the Adempas group were syncope (2%), gastritis (1%), acute renal failure (1%), and hypotension (1%). Common adverse effects that occurred more often in the riociguat group included headache (25%), dizziness (23%), dyspepsia (18%), and nasopharyngitis (15%).

PULMONARY ARTERIAL HYPERTENSION - STUDY 2

STUDY DESIGN	Randomized, multicenter, double-blind, placebo-controlled, phase 3 study (n=443).
INCLUSION CRITERIA	Adult patients with symptomatic PAH.
EXCLUSION	Patients receiving phosphodiesterase type 5 inhibitors.

CRITERIA	
TREATMENT REGIMEN	Participants (mean age, 51 +/- 17 years; 79% female) were randomized to 12 weeks of Adempas titrated up to 1.5 mg (exploratory dose; n=63), Adempas titrated up to 2.5 mg (n=254), or placebo (n=126) 3 times/day. Adempas was initiated at 1 mg 3 times/day and titrated every 2 weeks up to the target dose, based on systolic arterial blood pressure and signs or symptoms of hypotension. Forty-four percent of patients continued to receive treatment with an endothelin receptor antagonist and 6% with a prostacyclin analogue. In the group allocated to Adempas 2.5 mg 3 times/day, approximately 75% of patients achieved the target dose, while 15%, 6%, 3%, and 2% were titrated to Adempas doses of 2 mg, 1.5 mg, 1 mg, and 0.5 mg 3 times/day, respectively.
RESULTS	At baseline, most patients were at WHO functional class II (42%) or class III (53%), with a mean baseline 6MWD of 363 +/- 69 m among all patients. The change in 6MWD from baseline to 12 weeks (primary endpoint) was a mean increase of 30 m in the group who received Adempas 2.5 mg 3 times/day, compared with a mean decrease of 6 m in the placebo group (mean difference, 36 m; 95% CI, 20 to 52 m; $p < 0.001$). Compared with the placebo arm, the Adempas 2.5 mg 3 times/day arm had a significant decrease in pulmonary vascular resistance (mean difference, -226 dyn x sec/cm(5); 95% CI, -281 to -170 dyn x sec/cm(5); $p < 0.001$) and NT-proBNP level (mean difference, -432 pg/mL); 95% CI, -782 to -82 pg/mL; $p < 0.001$) from baseline to week 12. Patients in the Adempas 2.5 mg 3 times/day group also demonstrated significantly fewer events of clinical worsening compared with placebo (1% versus 6%, respectively; p=0.005), and a greater incidence of improvement in WHO functional class compared with placebo (21% versus 14%, respectively; p=0.003).
SAFETY	Serious adverse events due to Adempas were syncope (1%), elevated hepatic enzyme levels (0.4%), and acute renal failure (0.4%). Common adverse events due to riociguat included headache (27%), dyspepsia (19%), and peripheral edema (17%).

Contraindications[1]

- Concomitant use with nitrates, nitric oxide donors (eg, amyl nitrate), or phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors such as sildenafil or tadalafil and nonspecific inhibitors such as dipyridamole or theophylline
- Pregnancy; may cause fetal harm

Warnings and Precautions[1]

- Female patients of reproductive potential; may cause fetal harm; exclude pregnancy prior to, monthly during, and 1 month after treatment; prevent pregnancy with highly effective contraception.
- Special restricted distribution program under REMS due to potential for serious birth defects; prescribers, female patients, and pharmacies are required to enroll.
- Bleeding, serious; hemoptysis, hematemesis, subdural hematoma, and intra-abdominal, vaginal, and catheter site hemorrhages have been reported.
- Hypotension, symptomatic; increased risk in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors; dose reduction may be warranted.
- Pulmonary veno-occlusive disease (PVOD); may worsen cardiovascular status; use not recommended.
- Pulmonary edema; discontinue treatment if associated with PVOD.

Adverse Effects[1]

Most common, >= 3%	Adempas (n=490)	Placebo (n=214)
▪ Headache	27%	18%
▪ Dyspepsia/gastritis	21%	8%
▪ Dizziness	20%	13%
▪ Nausea	14%	11%
▪ Diarrhea	12%	8%
▪ Hypotension	10%	4%
▪ Vomiting	10%	7%
▪ Anemia	7%	2%
▪ Gastroesophageal reflux disease	5%	2%
▪ Constipation	5%	1%

Drug Interactions[1]

- Amyl nitrate
- Antacids
- CYP3A inhibitors, strong: ketoconazole, itraconazole, ritonavir
- CYP3A inducers, strong: carbamazepine, rifampin, phenobarbital, phenytoin
- Nitrates
- P-glycoprotein/Breast Cancer Resistance Protein (BCRP) inhibitors: ketoconazole, itraconazole, ritonavir
- Phosphodiesterase-5 inhibitors: sildenafil, tadalafil, vardenafil
- Phosphodiesterase inhibitors, nonspecific: dipyridamole, theophylline

Dosage and Administration[1]

The recommended starting dose is 1 mg orally 3 times daily; titrate by 0.5 mg 3 times daily every 2 weeks if tolerated up to 2.5 mg 3 times daily. Dosage adjustment may be necessary for hypotension, smokers, and patients receiving concomitant strong CYP450 and P-glycoprotein/BCRP inhibitors.

Cost

The cost per tablet, regardless of strength, is $84.17 each. MaximumAllowableCost

Conclusion

Efficacy of Adempas was established in two phase 3, randomized, double-blind, placebo-controlled trials. In each trial, riociguat improved exercise capacity and pulmonary vascular resistance. In patients with symptomatic PAH, Adempas was effective both as monotherapy and in patients who were receiving concomitant endothelin receptor antagonists or prostanoid agents. Female patients, along with prescribers and pharmacies, must enroll in a REMS program to mitigate the potential for embryofetal toxicity.

Recommendation

The Division recommends this product be considered for inclusion to the state specific PDL edit and it is currently under solicitation.

References

1. Product Information: Adempas®, riociguat. Bayer HealthCare Pharmaceuticals Inc, Whippany, NJ, 10/2013.

2. Ghofrani HA, D'Armini AM, Grimminger F et al: Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013; 369(4):319-329.

3. Ghofrani HA, Galie N, Grimminger F et al: Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013; 369(4):330-340.

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