Prognostic Evaluation and Risk Assessment in Pulmonary Arterial Hypertension (WHO Group 1)

Adapted from 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

INDICATIONS

- Adempas (riociguat) tablets is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve 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 predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61 %) or PAH associated with connective tissue diseases (25 %).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD, and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and one month after stopping treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

For important risk and use information, please see additional Important Safety Information throughout, and please access the full Prescribing Information, including Boxed Warning, at http://www.adempas-us.com/PI/.

BAYER

Adempas®
riociguat tablets
0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

Suggested Timing and Assessment for the Follow-up for Patients with PAH[1]

Adapted from 2015 ESC/ERS Guidelines[1]*

	At baseline	Every 3-6 months†	Every 6-12 months†	3-6 months after changes in therapy†	In case of clinical worsening
Medical assessment and determination of WHO FC	✓	✓	✓	✓	✓
ECG	✓	✓	✓	✓	✓
6MWT/Borg dyspnea score	✓	✓	✓	✓	✓
CPET	✓		✓		✓¶
Echo	✓		✓	✓	✓
Basic lab‡	✓	✓	✓	✓	✓
Extended lab§	✓		✓		✓
Blood gas analysis‖	✓		✓	✓	✓
RHC	✓		✓#	✓¶	✓¶

6MWT = six-minute walk test
ALAT = alanine aminotransferase
ASAT = aspartate aminotransferase
BGA = blood gas analysis
BNP = brain natriuretic peptide
CPET = cardiopulmonary exercise testing
Echo = echocardiography
ECG = electrocardiogram
ERA = endothelin receptor antagonists
INR = international normalized ratio
lab = laboratory assessment
NT-proBNP = N-terminal pro-brain natriuretic peptide
PAH = pulmonary arterial hypertension
RHC = right heart catheterization
TSH = thyroid stimulating hormone
WHO FC = World Health Organization functional class

***Adempas does not impact all of these measures.**

†Intervals to be adjusted according to patient needs.
‡Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP.
§Extended lab includes TSH, troponin, uric acid, iron status (iron,ferritin, soluble transferrin receptor) and other variables according to individual patient needs.
‖From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.
¶Should be considered.
#Some centers perform RHCs at regular intervals during follow-up.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Based on data from animal reproduction studies, Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.
- Patients with Pulmonary Hypertension associated with Idiopathic Interstitial Pneumonias (PH-IIP).

For important risk and use information, please see additional Important Safety Information throughout, and please access the full Prescribing Information, including Boxed Warning, at http://www.adempas-us.com/PI/.

Risk Assessment in PAH

Adapted from 2015 ESC/ERS Guidelines[1§§]

Determinants of prognosis**	Low risk	Intermediate risk	High risk
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope††	Repeated syncope‡‡
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope≥45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/mL	BNP <50-300 ng/L NT-proBNP 300-1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mm Hg CI <2.0 L/min/m^2 SvO_2 <60%

6MWD = 6-minute walking distance
BNP = brain natriuretic peptide
CI = cardiac index
CMR = cardiac magnetic resonance
NT-proBNP = N-terminal pro-brain natriuretic peptide
pred. = predicted
m = meters
RA = right atrium
RAP = right atrial pressure
SvO_2 = mixed venous oxygen saturation
VE/VCO_2 = ventilatory equivalents for carbon dioxide
VO_2 = oxygen consumption
WHO = World Health Organization

**Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

††Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

‡‡Repeated episodes of syncope, even with little or regular physical activity.

§§Adempas does not impact all of these measures.

For efficacy and safety information including monitoring, please see the full prescribing information.

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Based on data from animal reproduction studies, Adempas may cause embryo-fetal toxicity when administered to a pregnant female and is contraindicated in females who are pregnant. Advise females of reproductive potential of the potential risk to a fetus. Obtain a pregnancy test before the start of treatment, monthly during treatment, and for one month after stopping treatment. Advise females of reproductive potential to use effective contraception during treatment with Adempas and for at least one month after the last dose.

For females, Adempas is only available through a restricted program under the Adempas REMS Program.

For important risk and use information, please see additional Important Safety Information throughout, and please access the full Prescribing Information, including Boxed Warning, at http://www.adempas-us.com/PI/.

WARNINGS AND PRECAUTIONS (continued)

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia 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. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter-site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension, and peripheral edema.

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Reference: 1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;37:67-119.

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