PAH WHO GROUP 1

Risk Assessment at Diagnosis and Follow-Up in Pulmonary Arterial Hypertension

Adapted from 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

INDICATIONS

- Adempas (riociguat) 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/.

ERS = European Respiratory Society; ESC = European Society of Cardiology.

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2022 ESC/ERS PH Guidelines: Comprehensive risk assessment in PAH (3-Strata model)[1]

Assessing risk at diagnosis per the 2022 ESC/ERS guidelines

In the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, risk assessment of PAH patients is split into 2 treatment models—an updated 3-strata model, which is recommended for assessing risk at diagnosis, and the newer 4-strata model, which is recommended for assessing risk at follow-up (see following page). The 3-strata model, shown in the chart below, can help determine treatment escalation, risk assessment, and general treatment strategies.

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5-20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	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	Peak VO_2 <11 mL/min/kg (<35 % pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mm Hg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mm Hg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mm Hg Moderate or large pericardial effusion
cMRI[e]	RVEF >54 % SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54 % SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37 % SVI <26 mL/m^2 RVESVI >54 mL/m^2
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65 %	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65 %	RAP >14 mm Hg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60 %

[a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.
[b]Repeated episodes of syncope even with little or regular physical activity.
[c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.
[d]To harmonize with the four-strata model shown in the 2022 ERS/ESC guidelines, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels.
[e]cMRI parameters adapted from the 2022 ESC/ERS guidelines.

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; cMRI = cardiac magnetic resonance imaging; CPET = cardiopulmonary exercise testing; HF = heart failure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; pred = predicted; RA = right atrium; RAP = right atrial pressure; sPAP = systolic pulmonary arterial pressure; SvO_2 = mixed venous oxygen saturation; RVESVI = right ventricular end-systolic volume index; RVEF = right ventricular ejection fraction; SVI = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen uptake; WHO FC = World Health Organization Functional Class.

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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2022 ESC/ERS PH Guidelines: Risk assessment at follow-up (4-Strata model)[1]

The 4-strata (low, intermediate-low, intermediate-high, and high risk) model is based on WHO FC, 6MWD, and BNP or NT-proBNP, which is recommended for assessing risk at follow-up; additional variables should be considered as needed (eg, right heart imaging, hemodynamics). At any stage, individual factors (eg, age, sex, disease type, comorbidities, kidney function) should also be considered.

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO FC	I or II[a]	-	III	IV
6MWD	>440 m	320–440 m	165–319 m	<165 m
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

[a]WHO FC I and II are assigned 1 point as both are associated with good long-term survival.

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; WHO FC = World Health Organization Functional Class. Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.

Suggested Assessment and Timing for Follow-Up of Patients With PAH[1]

	At baseline	3–6 months after changes in therapy[a]	Every 3–6 months in stable patients[a]	In case of clinical worsening
Medical assessment (including WHO FC)	●	●	●	●
6MWT	●	●	●	●
Blood test (including NT-proBNP)[b,c]	●	●	●	●
ECG	●	●	●	●
Echocardiography or cMRI	●	●	●	●
ABG or pulse oximetry[d]	●	●	●	●
Disease-specific HR-QoL	●	●	●	●
CPET	●	●	●	●
RHC	●	●	●	●

Orange = is indicated; red = should be considered; blue = may be considered.

[a]Intervals to be adjusted according to patient needs, PAH etiology, risk category, demographics, and comorbidities.
[b]Basic laboratory tests include blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT, bilirubin, and BNP/NT-proBNP.
[c]Extended laboratory tests (eg, TSH, troponin, uric acid, iron status) according to clinical circumstances.
[d]ABG should be performed at baseline but may be replaced by pulse oximetry in stable patients at follow-up.

6MWT = 6-minute walk test; ABG = arterial blood gas analysis; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; cMRI = cardiac magnetic resonance imaging; CPET = cardiopulmonary exercise testing; ECG = electrocardiogram; HR-QoL = health-related quality of life; INR = international normalized ratio; 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.

IMPORTANT SAFETY INFORMATION (CONT'D)

- 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 concomitant use of other soluble guanylate cyclase (sGC) stimulators.
- Patients with Pulmonary Hypertension associated with Idiopathic Interstitial Pneumonias (PH-IIP).

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Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning.

Learn about setting and tracking your PAH patients' goals by visiting **Adempashcp.com**

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

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.

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/.

Reference:
1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;00:1-114.

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