Abbreviations

6MWD, 6-minute walking distance; AE, adverse event; cGMP, cyclic guanosine monophosphate; ERA, endothelin receptor antagonist; ESC, European Society of Cardiology; ERS, European Respiratory Society; NO, nitric oxide; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitors; RCT, randomized controlled trial; RRS, REVEAL risk score; SAE, serious adverse event; sGC, soluble guanylate cyclase; tid, three times a day; WHO FC, World Health Organization functional class.

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Adempas® 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg film-coated tablets.
Refer to full SmPC before prescribing.

▼ **This medicinal product is subject to additional monitoring.**
Adverse events should be reported. Please report any suspected adverse reaction to [enter name of national authority]. Website: [enter link to applicable national authority webpage, for example 'www.mhra.gov.uk/yellowcard' for UK].[1]
Composition: Each film-coated tablet contains 0.5 mg/1.0 mg /1.5 mg/2.0 mg/2.5 mg of Adempas. Excipients with known effect: Each film-coated tablet contains 37.8 mg/37.2 mg/36.8 mg/36.3 mg/35.8 mg lactose (as monohydrate). ***Excipients***[2]: cellulose microcrystalline, crospovidone, hypromellose, magnesium stearate, lactose monohydrate, sodium lauril sulfate, hydroxypropylcellulose, hypromellose, propylene glycol and titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172).
Indication: Chronic thromboembolic pulmonary hypertension (CTEPH): Adempas is indicated for the treatment of adult patients with WHO Functional Class (WHO FC) II to III with inoperable CTEPH, or persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity. Pulmonary arterial hypertension (PAH): Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with PAH with WHO FC II to III to improve exercise capacity. Efficacy has been shown in a PAH population including etiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease. **Contraindications:** Co-administration with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil), severe hepatic impairment (Child Pugh C), hypersensitivity to the active substance or to any of the excipients, pregnancy, co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called "poppers", patients with systolic blood pressure below 95 mmHg at treatment initiation, patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP). **Warnings and precautions:** In PAH, studies with Adempas have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of Adempas in other forms of PAH not studied is not recommended. In CTEPH, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with Adempas. Pulmonary veno-occlusive disease (PVOD): Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with 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 treatment with Adempas should be discontinued. Respiratory tract bleeding: In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. Careful monitoring of patients taking anticoagulants, according to common medical practice, is recommended. The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with Adempas, especially in the presence of risk factors, such as recent episodes of serious hemoptysis including those managed by bronchial arterial embolization. Adempas should be avoided in patients with a history of serious hemoptysis or who have previously undergone bronchial arterial embolization. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit:risk of treatment continuation. Hypotension: Adempas has vasodilatory properties which may result in lowering of blood pressure. Before prescribing Adempas, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolemia, severe left ventricular outflow obstruction, or autonomic dysfunction). Adempas must not be used in patients with a systolic blood pressure below 95 mmHg. Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering Adempas in these patients. Renal impairment: Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis, therefore Adempas is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased Adempas exposure in these patients. There is a higher risk of hypotension in these patients, and particular care should be exercised during individual dose titration. Hepatic impairment: There is no experience in patients with severe hepatic impairment (Child Pugh C); Adempas is contraindicated in these patients. PK data show that higher Adempas exposure was observed in patients with moderate hepatic impairment (Child Pugh B). Particular care should be exercised during individual dose titration. There is no clinical experience with Adempas in patients with elevated liver aminotransferases (>3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (>2 x ULN) prior to initiation of treatment; Adempas is not recommended in these patients. Pregnancy/contraception: Adempas is contraindicated in pregnancy. Therefore, female patients at potential risk of pregnancy must use an effective method of contraception. Monthly pregnancy tests are recommended. Smokers: Plasma concentrations of Adempas in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with Adempas. Concomitant use with other medicinal products: The concomitant use of Adempas with strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in Adempas exposure. The concomitant use of Adempas with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/BCRP inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase Adempas exposure. These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of Adempas be considered. Pediatric population: The safety and efficacy of Adempas in children and adolescents below 18 years have not been established. The use of Adempas in children and in growing adolescents should be avoided. Information about excipients: Each 0.5 mg film-coated tablet contains 37.8 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product. **Undesirable effects:** The safety of Adempas has been evaluated in Phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of Adempas. Serious hemoptysis and pulmonary hemorrhage, including cases with fatal outcome, have been observed in patients with CTEPH or PAH treated with Adempas. Adverse reactons reported with Adempas in the Phase III studies are listed by MedDRA system organ class and by frequency. ***Very common*** (≥1/10): headache, dizziness, dyspepsia, peripheral edema, nausea, diarrhea, and vomiting. ***Common*** (≥1/100 to <1/10): gastroenteritis, anemia (incl. respective laboratory parameters), palpitations, hypotension, hemoptysis, epistaxis, nasal congestion, gastritis, gastroesophageal reflux disease, dysphagia, gastrointestinal and abdominal pain, constipation, and abdominal distension. ***Uncommon*** (≥1/1,000 to <1/100): pulmonary hemorrhage. **On prescription only. Marketing Authorisation Holder:** Bayer AG, 13342 Berlin, Germany. **Date of revision of the underlying Prescribing Information:** February 2017

[1]*The exact wording of this statement is subject to national legislation.*
[2]*List of excipients should only be included when required according to national legislation.*

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REPLACE

Riociguat r**E**placing **P**DE5i therapy eva**L**uated **A**gainst **C**ontinued PDE5i th**E**rapy

Riociguat

A prospective, randomized, international, multicenter, double-arm, controlled, 24-week, open-label Phase IV study assessing the effect of switching to riociguat compared with maintenance of stable PDE5i in patients with PAH at intermediate risk

Rationale for REPLACE

There is a need for novel treatment strategies in patients with PAH

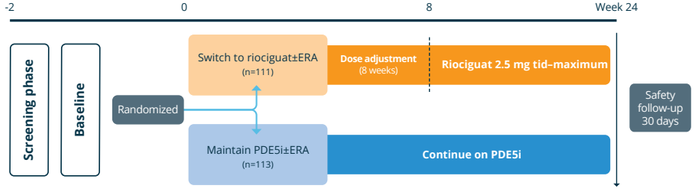
- ESC/ERS guidelines state that the goal of treatment should be to achieve/maintain a low-risk profile (good long-term prognosis).[1]
- Some patients with PAH, treated with PDE5i, still have an intermediate-risk profile,[2,3] which is considered an inadequate treatment response.[1]

Switching from a PDE5i to riociguat could address this need

- NO levels in patients with PAH decrease over time and with increasing severity of PAH. PDE5i depend on NO for their activity,[4–7] unlike riociguat, which functions independently of it,[8–11] offering an alternative treatment strategy for patients with an inadequate response to PDE5i.[a]

Study design and patient population

A prospective, randomized, international, multicenter, double-arm, controlled, 24-week, open-label Phase IV study



Patient population

Patients treated with a stable dose of PDE5i±ERA for ≥6 weeks, at intermediate risk

Intermediate risk, as indicated by:

- WHO FC III
- 6MWD 165–440 m

Primary endpoint (composite, centrally adjudicated)

- **Clinical improvement at Week 24, defined as 2 out of 3:**
  - 6MWD improvement by ≥10% or ≥30 m
  - WHO FC I/II
  - NT-proBNP decrease by ≥30%
- **Absence of clinical worsening**

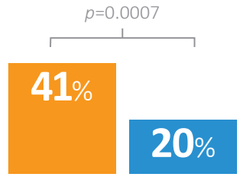
[a]Concomitant use of riociguat with PDE5i is contraindicated.[12]
[b]Secondary endpoints were not powered to show an effect.
[c]The risk profiles for the patient groups were similar at baseline.
[d]The French non-invasive scale refers to the number of parameters in the low-risk range.

REPLACE study results

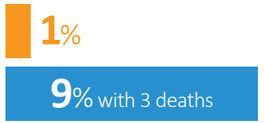
Switching from PDE5i to riociguat had a significantly higher likelihood of clinical improvement and significantly reduced rate of clinical worsening compared with patients remaining on PDE5i

Riociguat
PDE5i

Primary endpoint

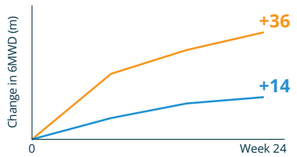


Clinical worsening in patients not achieving the endpoint (p=0.0047)



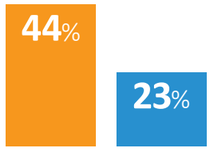
Secondary endpoints[b]

6MWD



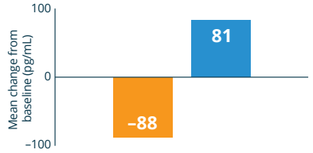
p=0.0542

Patients with improved WHO FC



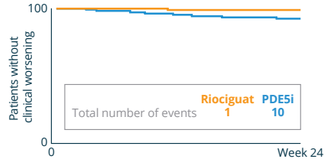
p=0.0007

NT-proBNP



p=0.1067

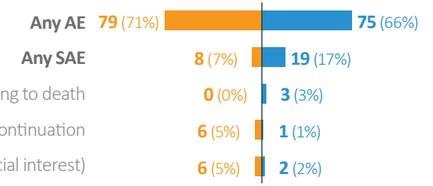
Time to clinical worsening



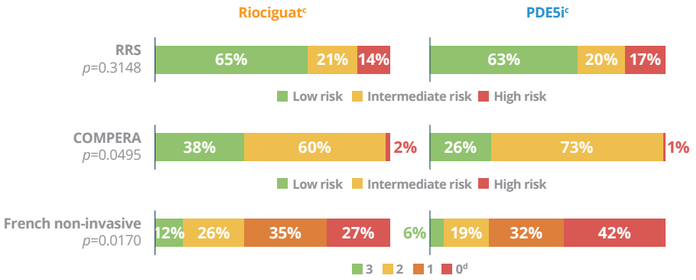
p=0.0070

Safety

No new safety signals



Risk profiles at Week 24



- REPLACE is the first randomized, controlled study in patients with PAH investigating switching within the same pathway, and also the first head-to-head RCT of approved PAH therapies
- Riociguat was generally well tolerated in patients who switched from PDE5i. Overall AE rates were similar between the treatment groups, with a higher incidence of SAEs in the PDE5i group
- REPLACE demonstrated that switching from PDE5i (±ERA) to riociguat can benefit patients with PAH at intermediate risk and can serve as a strategic option for treatment escalation
- By optimizing the NO–sGC–cGMP pathway by switching from PDE5i to riociguat, patients can remain on monotherapy or dual combination therapy, delaying the addition of further therapies to a later stage