PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrADEMPAS®

riociguat (film-coated) tablet

Tablet, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg for oral use

Professed standard

Soluble Guanylate Cyclase (sGC) Stimulator

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	10/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Pulmonary Hypertension

ADEMPAS (riociguat) is indicated for the treatment of:

- inoperable chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4)
- persistent or recurrent CTEPH after surgical treatment
- pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists

in adult patients (≥18 years of age) with WHO Functional Class II or III pulmonary hypertension.

ADEMPAS should only be used by clinicians experienced in the diagnosis and treatment of CTEPH or PAH.

1.1 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established (see 7.1.3 Pediatrics). Therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population (up to 80 years of age) is associated with increases in some adverse events (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Concomitant use of ADEMPAS with other drugs affecting the nitric oxide-soluble guanylate cyclase- cyclic guanosine monophosphate (NO-sGC-cGMP) pathway is contraindicated, due to the risk of developing potentially life-threatening episodes of hypotension or syncope.

  These drugs include:

  - **Phosphodiesterase type 5** (PDE5) inhibitors, such as sildenafil, tadalafil, vardenafil
  - **Nitrates**, taken either regularly or intermittently, in any form (e.g. oral, sublingual, transdermal, by inhalation)
  - **Nitric oxide donors**, such as amyl nitrite (See 9.4 Drug-Drug Interactions)
- Concomitant use with other soluble guanylate cyclase stimulators is contraindicated (see 9.4 Drug-Drug Interactions).
- ADEMPAS is contraindicated during pregnancy and nursing (see 7.1.2 Breast-feeding and 16 NON-CLINICAL TOXICOLOGY).
- Hypersensitivity to ADEMPAS or to any ingredient in the formulation (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- ADEMPAS is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment should only be initiated and monitored under the supervision of a clinician experienced in the diagnosis and treatment of CTEPH or PAH.

4.2 Recommended Dose and Dosage Adjustment

Treatment Initiation

The recommended starting dose of ADEMPAS is 1 mg 3 times daily for 2 weeks. Tablets should be taken 3 times daily approximately 6 to 8 hours apart, with or without food. A lower starting dose of 0.5 mg 3 times daily may be used at the discretion of the physician to minimize the potential of hypotensive events.

Dosage should be increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg 3 times daily, if systolic blood pressure is ≥95 mmHg and the patient has no signs or symptoms of hypotension. If systolic blood pressure falls below 95 mmHg, dosage should be maintained provided the patient does not show any signs or symptoms of hypotension. If, at any time during the up-titration phase, systolic blood pressure decreases below 95 mmHg, and the patient shows signs or symptoms of hypotension, the next 3 doses should be withheld and dosing should be restarted, decreased by 0.5 mg three times daily, 24 hours later, as clinically warranted.

Maintenance Dose

The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose of ADEMPAS is 7.5 mg.

If not tolerated, dose reduction might be considered at any time.

Treatment Discontinuation

In case treatment has to be interrupted for 3 days or more, restart treatment at the starting dose 3 times daily for 2 weeks, and continue dose titration regimen as described above.

Transitioning between PDE5 inhibitors and Riociguat

Discontinue sildenafil at least 24 hours or tadalafil at least 48 hours prior to administering riociguat. Begin treatment with ADEMPAS as normally recommended (see 4.2 Recommended Dose and Dosage Adjustment – Treatment Initiation). Discontinue ADEMPAS at least 24 hours prior to administering a PDE5 inhibitor. It is recommended to monitor for signs and symptoms of hypotension after any transition (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions).

A 24-week, uncontrolled study investigated the transition from PDE5 inhibitors, sildenafil or tadalafil, to ADEMPAS, in 61 adult PAH patients stable on PDE5 inhibitors. All patients were WHO Functional Class III and 82% received background therapy with an endothelin receptor antagonist (ERA). All patients in the study were transitioned from sildenafil (up to 80 mg tid) or tadalafil (up to 40 mg od) to 1 mg three times daily ADEMPAS (median treatment-free washout period of 1 day for sildenafil and 3 days for tadalafil). Overall, the safety profile observed in the study was comparable with that observed in the pivotal trials, with no serious adverse events reported during the transition period. Six patients (10%) experienced at least one clinical worsening event, including 2 deaths unrelated to study drug.

Geriatrics (≥65 years of age)

Elderly (≥65 years) patients exhibited higher plasma concentrations than younger patients. Particular care should be exercised during individual dose titration (see 10.3 Pharmacokinetics – Special Populations and Conditions: Geriatrics).

Pediatrics

Safety and effectiveness in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

Hepatic Impairment

Particular care should be exercised during individual dose titration in patients with moderate hepatic impairment (Child Pugh B) (see 10.3 Pharmacokinetics, Special Populations and Conditions: Hepatic Insufficiency).

ADEMPAS is not recommended in patients with severe hepatic impairment (Child Pugh C) (see 7.1 Special Populations).

Renal Impairment

Particular care should be exercised during individual dose titration in patients with mild, moderate, or severe renal impairment (creatinine clearance 15 to 80 mL/min) (see 10.3 Pharmacokinetics, Special Populations and Conditions: Renal Insufficiency).

ADEMPAS is not recommended in patients with creatinine clearance <15 mL/min or on dialysis (see 7.1 Special Populations).

Smoking Status

Current smokers should be advised to stop smoking. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment of ADEMPAS may be required in patients who stop or start smoking during treatment (see 9.2 Drug Interactions Overview and 10.3 Pharmacokinetics – Metabolism).

Concomitant Use with Antacids

Antacids should be taken at least 1 hour after ADEMPAS (see 9.2 Drug Interactions Overview).

Strong CYP and P-gp/BCRP Inhibitors

Coadministration of ADEMPAS with strong multipathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to ADEMPAS (see 9.2 Drug Interactions Overview). Consider a starting dose of 0.5 mg, three times when initiating ADEMPAS in patients on stable doses of strong multipathway CYP and P-gp/BCRP inhibitors to mitigate risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong multipathway CYP and P-gp/BCRP inhibitors. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors and 9.2 Drug Interactions Overview).

4.5 Missed Dose

If a dose is missed, the next dose should be taken as scheduled. The dose should not be doubled to make up for the missed dose.

5 OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

Inadvertent overdosing with total daily doses of 9 to 25 mg ADEMPAS between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see 8 ADVERSE REACTIONS).

No specific antidote exists.

In case of overdose, standard supportive measures should be adopted as required.

In case of pronounced hypotension, active cardiovascular support may be required.

Based on the high plasma protein binding riociguat is not expected to be dialyzable.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage forms, strengths, composition and packaging

Route of Administration	Dosage Form, Strength	Nonmedicinal Ingredients
Oral	Film-coated tablet, 0.5 mg	cellulose microcrystalline, crospovidone, hydroxypropylcellulose, hypromellose 3cP, hypromellose 5cP, lactose monohydrate, magnesium stearate, propylene glycol, sodium laurilsulphate and titanium dioxide
	Film-coated tablet, 1 mg, 1.5 mg	cellulose microcrystalline, crospovidone, ferric oxide yellow, hydroxypropylcellulose, hypromellose 3cP, hypromellose 5cP, lactose monohydrate, magnesium stearate, propylene glycol, sodium laurilsulphate and titanium dioxide
	Film-coated tablet, 2.0 mg and 2.5mg	cellulose microcrystalline, crospovidone, ferric oxide red, ferric oxide yellow, hydroxypropylcellulose, hypromellose 3cP, hypromellose 5cP, lactose monohydrate, magnesium stearate, propylene glycol, sodium laurilsulphate and titanium dioxide

ADEMPAS tablets are film-coated, round, and marked with the Bayer cross on one side:

- 0.5 mg white tablets marked with “0.5” and an “R” on the other side.
- 1 mg pale yellow tablets marked with “1” and an “R” on the other side.
- 1.5 mg yellow-orange tablets marked with “1.5” and an “R” on the other side.
- 2 mg pale orange tablets marked with “2” and an “R” on the other side.
- 2.5 mg red-orange tablets marked with “2.5” and an “R” on the other side.

ADEMPAS 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets are supplied in HDPE bottles of 42 and 90 and in blisters of 42.

7 WARNINGS AND PRECAUTIONS

General

Concomitant Use with CYP or P-gp/BCRP Inhibitors

The concomitant use of ADEMPAS with strong multi pathway CYP and P-gp/BCRP inhibitors, such as azole antimycotics (eg, ketoconazole, itraconazole), or HIV protease inhibitors (eg, ritonavir) results in a pronounced increase in riociguat exposure (see 9.4 Drug-Drug Interactions), and may result in hypotension.

Assess the benefit-risk for each patient individually before prescribing ADEMPAS in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors. Consider a starting dose of 0.5 mg ADEMPAS, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment and consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 4 DOSAGE AND ADMINISTRATION, Strong CYP and P-gp/BCRP Inhibitors and 9.4 Drug-Drug Interactions). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

The concomitant use of ADEMPAS with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, or strong P-gp/BCRP inhibitors, such as the immunosuppressant cyclosporine A, may result in increased riociguat exposure (see 9.4 Drug-Drug Interactions). These drugs should be used with caution when co-administered with ADEMPAS. Blood pressure should be monitored and dose reduction of ADEMPAS might be considered.

Drugs Affecting the NO-sGC-cGMP Pathway

ADEMPAS and other drugs that result in increased levels of intracellular cGMP act as vasodilators. Additive or synergistic effects on systemic blood pressure should be anticipated. Concomitant use of PDE5-inhibitors, nitrates or nitric oxide donors is contraindicated (see 2 CONTRAINDICATIONS).

Effect of Cigarette Smoking

In cigarette smokers, riociguat exposure is reduced by 50 to 60% (see 10.3 Pharmacokinetics – Metabolism). Therefore patients are advised to stop smoking. Dose adjustment of ADEMPAS may be required in patients who stop or start smoking during treatment (see 4.2 Recommended Dose and Dosage Adjustment).

Bleeding

In patients with pulmonary hypertension there is an increased likelihood of bleeding, particularly among patients receiving anticoagulation therapy. Bleeding risk should be carefully evaluated before initiating ADEMPAS therapy, and should be monitored periodically, particularly in patients taking anticoagulants. The risk of serious and fatal bleeding, including 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 the placebo-controlled clinical trials program, 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. In long-term extension studies, there was no evidence for temporal clustering of bleeding events throughout the period of treatment with ADEMPAS.

Patients should be instructed to notify the treating physician of any unexpected or excessive bleedings.

Cardiovascular

Hypotension

As a sGC stimulator, ADEMPAS acts as a vasodilator, lowering both pulmonary and systemic blood pressure. The demonstrated risk of hypotension should be carefully considered (see 8 ADVERSE REACTIONS), in particular in patients with concomitant or underlying conditions such as low systemic blood pressure (e.g., systolic blood pressure < 95 mmHg), coronary artery disease (CAD), hypovolemia, resting hypotension, severe left ventricular outflow obstruction, autonomic dysfunction, as well as in patients on concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors) .

Driving and operating machinery

Dizziness has been reported and may affect the ability to drive and use machines. Patients should be aware of how they react to ADEMPAS, before driving or operating machinery.

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 treatment with ADEMPAS should be discontinued.

7.1 Special Populations

ADEMPAS has not been studied in the following patient populations and its use is therefore not recommended in:

- Patients with systolic blood pressure <95 mm Hg at treatment initiation
- Patients with severe hepatic impairment (Child Pugh C)
- Patients with creatinine clearance <15 mL/min or on dialysis

7.1.1 Pregnant Women

There are no adequate data from the use of ADEMPAS in pregnant women. Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology:). Therefore, ADEMPAS is contraindicated in females who are or may become pregnant (see 2 CONTRAINDICATIONS). Women of childbearing potential should be advised to use effective contraception during treatment with ADEMPAS.

No specific studies with ADEMPAS in humans have been conducted to evaluate effects on fertility. In studies that evaluated male and female fertility in rats, no effects were seen with riociguat up to 5.1 times human exposure when corrected for species differences in protein binding, whereas its main metabolite produced a slight decrease in implantation rate at systemic exposure comparable to human systemic exposure (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology:).

7.1.2 Breast-feeding

No data on the use of ADEMPAS in breast-feeding women are available. Data from animals indicate that ADEMPAS is excreted into milk.

Because of the potential for serious adverse reactions in nursing infants, the use of ADEMPAS during breast-feeding is contraindicated (see 2 CONTRAINDICATIONS). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the importance of the drug for the mother.

7.1.3 Pediatrics

The safety and effectiveness of ADEMPAS in patients younger than 18 years of age has not been established in the CTEPH and PAH study programs., Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Forty-three percent (43%) of the ADEMPAS-treated patients in the CTEPH and 26% of the ADEMPAS-treated patients in the PAH study programs were 65 to 80 years of age. In contrast to younger patients, dizziness and hypotension occurred more frequently in these older patients when treated with ADEMPAS, compared to same-aged patients on placebo. Dose titrations should be performed with caution in this age group.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious hemoptysis and pulmonary hemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with ADEMPAS (see 7 WARNINGS AND PRECAUTIONS, Bleeding).

The most commonly reported adverse reactions, occurring in ≥10% of patients under ADEMPAS treatment (up to 2.5 mg tid) were headache, dizziness, dyspepsia, peripheral edema, nausea, diarrhea, and vomiting.

The safety of ADEMPAS has been evaluated in Phase III trials of more than 650 patients with CTEPH or PAH receiving at least 1 dose of ADEMPAS (see 14 CLINICAL TRIALS).

The overall rates of discontinuation due to an adverse event (AE) in these pooled pivotal placebo-controlled trials were 2.9% for ADEMPAS, and 5.1% for placebo.

Since ADEMPAS is a vasodilator, common to very common AEs in the pooled Phase III trials were dizziness, (pre)syncope and hypotension.

Dizziness occurred in 19.8% of patients on riociguat, compared to 13.1% of the placebo patients (see Table 4).

Hypotensive events occurred as AEs in 49 (10%) of the patients on riociguat - in 2 cases as a non-fatal SAE - and in 8 (3.7%) of the patients on placebo; in no case as an SAE (see Table 4).

Bleeding events were very common in the riociguat-treated patients in the pooled Phase III trials. Idiopathic bleeding events, i.e., events not caused by procedures, were observed in 58 (11.8%) of the riociguat-treated patients, of which 10 cases were noted as SAEs, 1 of which was fatal. In the placebo groups, 18 (8.4%) idiopathic bleeding events were observed, none as an SAE (see Table 4).

Anemia occurred commonly in the pooled Phase III trials. Anemia (or respective changes in laboratory values) reported as an AE was noted in 33 (6.7%) of the patients on riociguat, in 2 of these cases as an SAE. Anemia occurred in 5 (2.3%) of the patients on placebo, once as an SAE (see Table 4).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with ADEMPAS (CHEST-1 data)

System Organ Class	ADEMPAS % (n=173)	Placebo % (n=88)
Infections and Infestations		
Gastroenteritis	2.3	1.1
Blood and the lymphatic system disorders		
Bleeding (incl. epistaxis and hemoptysis)	12.7	9.1
Anemia (incl. respective laboratory parameters)	4.6	2.3
Nervous system disorders		
Headache	24.9	13.6
Dizziness	23.1	13.6
Cardiac disorders		
Palpitations	3.5	4.5
Vascular disorders		
Hypotension (incl. blood pressure decreased)	11.0	4.5
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	3.5	3.4
Gastrointestinal disorders		
Dyspepsia (incl. epigastric discomfort and eructation)	18.5	8.0
Nausea	11.0	8.0
Diarrhea	9.8	4.5
Vomiting	9.8	3.4
Gastrointestinal and abdominal pains	9.8	5.7
Gastrooesophageal reflux disease	4.0	0
Constipation	5.8	1.1
Gastritis	3.5	0
Dysphagia	3.5	0
Abdominal distension	1.2	0
General disorders and administration site conditions		
Edema peripheral	15.6	20.5

Table 3: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with ADEMPAS (PATENT-1 data)[*]

System Organ Class	ADEMPAS % (n=317)	Placebo % (n=126)
Infections and Infestations		
Gastroenteritis	2.5	0.8
Blood and the lymphatic system disorders		
Bleeding (incl. epistaxis and hemoptysis)	11.4	7.9
Anemia (incl. respective laboratory parameters)	7.9	2.4
Nervous system disorders		
Headache	28.1	20.6
Dizziness	18.0	12.7
Cardiac disorders		
Palpitations	7.9	4.8
Vascular disorders		
Hypotension (incl. blood pressure decreased)	9.1	3.2
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	4.7	2.4
Gastrointestinal disorders		
Dyspepsia (incl. epigastric discomfort and eructation)	18.6	8.7
Nausea	15.8	12.7
Diarrhea	13.2	10.3
Vomiting	10.4	8.7
Gastrointestinal and abdominal pains	9.1	7.9
Gastrooesophageal reflux disease	5.7	3.2
Constipation	3.8	1.6
Gastritis	2.5	0
Dysphagia	1.6	0
Abdominal distension	2.5	0.8
General disorders and administration site conditions		
Edema peripheral	18.3	11.1

* Pooled data from the Individual Dose Titration Group (1 to 2.5 mg tid) and the Capped Dose Group (1 to 1.5 mg tid)

Table 4: Treatment-Emergent Adverse Reactions Reported by ≥1% of Patients Treated with ADEMPAS (pooled CHEST-1 and PATENT-1 data)

System Organ Class	ADEMPAS % (n=490)	Placebo % (n=214)
Infections and infestations		
Gastroenteritis	2.4	0.9
Blood and the lymphatic system disorders		
Bleeding (incl. epistaxis and hemoptysis)	11.8	8.4
Anemia (incl. respective laboratory parameters)	6.7	2.3
Nervous system disorders		
Headache	26.9	17.8
Dizziness	19.8	13.1
Cardiac disorders		
Palpitations	6.3	4.7
Vascular disorders		
Hypotension	10.0	3.7
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	4.3	2.8
Gastrointestinal disorders		
Dyspepsia	18.6	8.4
Nausea	14.1	10.7
Diarrhea	12.0	7.9
Vomiting	10.2	6.5
Gastrointestinal and abdominal pains	9.4	7.0
Gastrooesophageal reflux disease	5.1	1.9
Constipation	4.5	1.4
Gastritis	2.9	0
Dysphagia	2.2	0
Abdominal distension	2.0	0.5
General disorders and administration site conditions		
Edema peripheral	17.3	15.0

8.3 Less Common Clinical Trial Adverse Reactions

Pulmonary hemorrhage was reported in ≤1% of patients treated during the long term extension studies with ADEMPAS.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Treatment-emergent values below the lower limit of normal for erythrocytes, hematocrit, and hemoglobin were observed more frequently in the riociguat group than in the placebo group.

In a pooled analysis of placebo-controlled Phase III studies in patients with CTEPH or PAH, changes from baseline in mean hemoglobin (-0.58 g/dL vs. 0.13 g/dL) and hematocrit (-1.66% vs. 0.45%) were observed in patients receiving ADEMPAS or placebo, respectively. Decreases in hemoglobin (24.1% vs. 9.1%) and hematocrit (13.3% vs. 4.9%) were observed in patients receiving ADEMPAS and placebo, respectively. Anemia had a higher rate in the ADEMPAS group (6.7%) compared to placebo (2.3%).

Mean changes in group values from baseline were small for most of the clinical chemistry parameters in the pooled controlled Phase III studies.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Phosphodiesterase type 5 (PDE5) inhibitors (such as sildenafil, tadalafil, vardenafil) • Nitrates • Nitric oxide donors • Other soluble guanylate cyclase stimulators See 9.4 Drug-Drug Interactions for detailed information.

9.2 Drug Interactions Overview

Effects of Other Substances on Riociguat

ADEMPAS is cleared mainly via biliary/direct fecal excretion of the unchanged drug, and renal excretion of the unchanged drug via glomerular filtration. ADEMPAS is mainly catalysed to its main metabolite M1 by several CYP isoforms (CYP1A1, CYP2J2, CYP3A4, CYP3A5). Based on *in vitro* studies, riociguat was found to be a substrate for the membrane transport proteins P-gp/BCRP. Inhibitors or inducers of these enzymes or transporters may affect riociguat exposure.

Riociguat exhibits a reduced solubility at neutral pH vs. acidic medium. Co-medication of drugs increasing the upper gastro-intestinal pH may lead to lower oral bioavailability.

Effects of Riociguat on Other Substances

Riociguat and its main metabolite are neither inhibitors nor inducers of major CYP isoforms (including CYP3A4) or transporters (eg, P-gp/BCRP) *in vitro* at therapeutic plasma concentrations.

Patients must not get pregnant during ADEMPAS therapy (see 2 CONTRAINDICATIONS). Riociguat (2.5 mg three times per day) did not have a clinically meaningful effect on the exposure of combined oral contraceptives containing levonorgestrel and ethinyl estradiol when concomitantly administered to healthy female subjects.

Riociguat and its main metabolite revealed to be strong **inhibitors of CYP1A1** *in vitro*. Therefore, clinically relevant drug-drug interactions with co-medications which are significantly cleared by CYP1A1-mediated biotransformation, such as erlotinib or granisetron, cannot be ruled out.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5: Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Nitrates	CT	ADEMPAS 2.5 mg tablets potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake.	Coadministration of ADEMPAS with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see 2 CONTRAINDICATIONS)
PDE5 inhibitors: - Sildenafil - Tadalafil - Vardenafil	CT	Studies in animal models showed additive systemic blood pressure lowering effect when ADEMPAS was combined with either sildenafil or vardenafil. With increased doses, over additive effects on systemic blood pressure were observed in some cases. In an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) single doses of ADEMPAS (0.5 mg and 1 mg sequentially) showed additive hemodynamic effects, but no pharmacodynamic advantages. Doses above 1 mg ADEMPAS were not investigated in this study. A 12-week combination study in 18 patients with PAH on stable sildenafil treatment (20 mg three times daily) and ADEMPAS (1 mg-2.5 mg three times daily) compared to sildenafil alone was performed. In the long-term extension part (non-controlled) the concomitant use of sildenafil and ADEMPAS resulted in a high rate of discontinuation, predominately due to hypotension. There was no evidence of a favorable clinical effect of the combination in the population studied.	Concomitant administration of ADEMPAS with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see 2 CONTRAINDICATIONS). For information on transitioning between ADEMPAS and PDE5 inhibitors (ie, tadalafil and sildenafil) see 4.2 Recommended Dose and Dosage Adjustment, Transitioning between PDE5 inhibitors and Riociguat.
Other Soluble Guanylate Cyclase Stimulators	T		Co-administration of Adempas with other soluble guanylate cyclase (sGC) stimulators is contraindicated (see 2 CONTRAINDICATIONS).

Proper Name	Ref	Effect	Clinical Comment
Antifungal Agents: - Ketoconazoles - Clotrimazole - Itraconazole - Miconazole	CT, I	Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean C_{max}. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h. Pronounced inhibition of recombinant human CYP1A1 by the antifungal agents was observed *in vitro* (ketoconazole, clotrimazole and miconazole, IC_{50} values of 0.3 to 0.6µm). *In vitro*, riociguat main metabolite M1 formation in human liver microsomes was also inhibited by the antifungal agents (ketoconazole > miconazole > clotrimazole, IC_{50} values of 0.6 to 5.7 µM). Ketoconazole and itraconazole showed inhibitory potency on P-gp/BCRP mediated efflux of riociguat *in vitro* (ketoconazole $[I_1]/IC_{50}$: 0.01, $[I_2]/IC_{50}$ >10; itraconazole $[I_1]/IC_{50}$: 0.3; $[I_2]/IC_{50}$ >10).	Due to limited clinical experience, ADEMPAS and multi pathway CYP or P-gp/BCRP inhibitors should be co-administered with caution. When initiating ADEMPAS therapy in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. ketoconazole or itraconazole, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Proper Name	Ref	Effect	Clinical Comment
Highly active antiretroviral therapy (HAART) including HIV protease inhibitors	I, CT	*In vitro*, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. *In vitro*, riociguat main metabolite M1 formation in human liver microsomes was considerably inhibited by HIV protease inhibitors (ritonavir, atazanavir > indinavir, IC_{50} values of 5.3 to 11.7 µM). Ritonavir and saquinavir showed inhibitory potency on P-gp/BCRP mediated efflux of riociguat *in vitro* ($[I_1]/IC_{50}$ >0.1 or $[I_2]/IC_{50}$>10). The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a pharmacokinetic drug-drug interaction study with HIV non-PAH patients. Concomitant administration of a stable regimen of varying HAART combinations with a single 0.5 mg dose of ADEMPAS led to an increase in ADEMPAS mean AUC and Cmax of up to about 160% and 30%, respectively in HIV non-PAH patients compared to a healthy historical control group. No new safety findings were observed in this single dose study.	Due to limited clinical experience, ADEMPAS and multi pathway CYP or P-gp/BCRP inhibitors should be co-administered with caution. When initiating ADEMPAS treatment in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. as contained in HAART therapy, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on ADEMPAS doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). In patients on stable doses of ADEMPAS, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.
Cyclosporine A	I	Based on *in vitro* studies, cyclosporine A inhibited efflux of riociguat mediated by the membrane transport proteins P-gp/BCRP (IC_{50}: 4 µM; $[I_1]/IC_{50}$ < 0.1, $[I_2]/IC_{50}$ > 10, respectively).	Drugs strongly inhibiting P-gp/BCRP, such as cyclosporine A, should be used with caution (see). Blood pressure should be monitored, and dose reduction of ADEMPAS should be considered. 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors)

Proper Name	Ref	Effect	Clinical Comment
Quinidine	I	Quinidine inhibited P-gp/BCRP mediated efflux of riociguat (IC_{50}: 19 µM, $[I_1]/IC_{50}$: 0.12, $[I_2]/IC_{50}$: 105 for P-gp, and IC_{50}: 300 µM, $[I_1]/IC_{50}$: 0.01, $[I_2]/IC_{50}$: 16 for BCRP, respectively).	Drugs strongly inhibiting P-gp/BCRP should be used with caution (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). Blood pressure should be monitored, and dose reduction of ADEMPAS should be considered.
Tyrosine kinase inhibitors - Erlotinib - Gefitinib	I, T	*In vitro*, pronounced inhibition of recombinant human CYP1A1 by tyrosine kinase inhibitors (eg, erlotinib, gefitinib, imatinib, sorafenib and sunitinib) was observed (IC_{50} values: 0.2 to 4.2 µM), and the tyrosine kinase inhibitors also affected the M1 formation in human liver microsomes (IC_{50} values: 6.9 to 20.1 µM).	Strong CYP1A1 inhibitors should be used with caution (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). Blood pressure should be monitored, and dose reduction of ADEMPAS should be considered.
Carvedilol	I, T	*In vitro*, pronounced inhibition of recombinant human CYP1A1 was observed (IC_{50} value: 0.7 µM); M1 formation in human liver microsomes was also affected (IC_{50} value: 11 µM).	Strong CYP1A1 inhibitors should be used with caution (see 7 WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors). Blood pressure should be monitored, and dose reduction of ADEMPAS should be considered.
Clarithromycin	CT	Co-administration of **clarithromycin** (500 mg twice daily), classified as strong and selective CYP3A4 inhibitor and also reported to be a weak-to-moderate P-gp inhibitor, moderately increased mean AUC by 41% without significant change in C_{max}. This is not considered clinically relevant.	No dose adjustment required.
H^+, K^+-ATPase (proton pump) inhibitor - Omeprazole - Pantoprazole	CT, I	Pre- and co-treatment with the proton pump inhibitor **omeprazole** (40 mg once daily) reduced riociguat mean AUC by 26% and mean C_{max} by 35% in healthy volunteers. This is due to increased gastric pH by omeprazole as anticipated from *in vitro* solubility data. Riociguat exhibits a reduced solubility at neutral pH vs. acidic medium *in vitro*. Pantoprazole reduced the BCRP mediated efflux of riociguat concentration dependent with an IC_{50} of 4.0 µM ($[I_1]/IC_{50}$: 1.5, $[I_2]/IC_{50}$: 100).	No dose adjustment required.
Aluminum hydroxide/ magnesium hydroxide	CT	Co-administration of the antacid **aluminum hydroxide / magnesium hydroxide** reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see 4 DOSAGE AND ADMINISTRATION).	Antacids should be taken at least 1 hour after ADEMPAS.

Proper Name	Ref	Effect	Clinical Comment
Amiodarone	I	Amiodarone inhibited P-gp mediated transport of riociguat across L-MDR1 cells (IC_{50}: 4.3 µM, $[I_2]/IC_{50}$: 277). Amiodarone showed a weak inhibition of the recombinant human CYP1A1 mediated M-1 formation with IC_{50} value of 4.9 µM.	No dose adjustment required.
Bosentan	CT	**Bosentan**, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% without compromising the efficacy of the combination.	No dose adjustment required.
Phenytoin, Carbamazepine, Phenobarbitone St. John's Wort	CT	The concomitant use of ADEMPAS with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbitone, or St. John's Wort) may also lead to decreased riociguat plasma concentration.	No dose adjustment required.
Verapamil	I	Verapamil inhibited P-gp mediated transport of riociguat across L-MDR1 cells (IC_{50}: 3.3 µM, $[I_2]/IC_{50}$: 92).	No dose adjustment required.
Warfarin/ Phenprocoumon	CT	Concomitant treatment with ADEMPAS and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of ADEMPAS with other coumarin-derivates (eg, phenprocoumon) is also not expected to alter prothrombin time. Lack of mutual pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.	No dose adjustment required.
Acetylsalicylic Acid (ASA)	CT	Riociguat did neither potentiate the bleeding time caused by acetylsalicylic acid nor affect the platelet aggregation in humans.	No dose adjustment required.
UGT1A1, UGT1A9 inhibitors	I,T	UGT1A1 and 1A9 are involved in the N-glucuronidation of metabolite M1 to M4. *In vitro*, the UGT1A1 inhibitor atazanavir, considerably reduced the M4 formation. In addition, the UGT1A9 inhibitor niflumic acid, inhibited the N-glucuronidation of M1. Thus, UGT1A1 and 1A9 inhibitors may potentially increase the exposure of M1, which is pharmacologically active (pharmacological activity: 1/10th to 1/3rd of riociguat).	Drugs strongly inhibiting UGT1A1 and/or UGT1A9 should be used with caution. Blood pressure should be monitored, and dose reduction of ADEMPAS should be considered. Concomitant use with atazanavir is not recommended (see HIV protease inhibitors in this table).

Legend: CT=Clinical Trial; I=*In Vitro* T=Theoretical

$[I_1]$: maximum steady-state inhibitor systemic concentration

$[I_2]$: hypothetical intestinal concentration (highest dose/250 mL)

9.5 Drug-Food Interactions

No clinically relevant interaction with food was observed (see 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

In cigarette smokers riociguat exposure is reduced by 50 to 60% (see 10.3 Pharmacokinetics - Metabolism). Therefore patients are advised to stop smoking (see 4.2 Recommended Dose and Dosage Adjustment, Smoking Status). Dose adjustment of ADEMPAS may be required in patients who stop or start smoking during treatment.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ADEMPAS is a stimulator of the soluble guanylate cyclase (sGC), an enzyme found in most mammalian cells including those of the cardiopulmonary system. sGC is also the receptor for nitric oxide (NO).

10.2 Pharmacodynamics

There is a direct relationship between riociguat plasma concentration and hemodynamic parameters such as systemic and pulmonary vascular resistance, systolic blood pressure, and cardiac output.

10.3 Pharmacokinetics

Table 6: Summary of Pharmacokinetic Parameters in Humans

	C_{max} (µg/L)	$t_{1/2}$ (h)	$AUC_{0-7/8}$ (µg*h/L)	Clearance/F (L/h)	C_{trough} (µg/L)
Single Dose Studies					
	119	11.7	1411	1.77	72.6
Multiple Dose Studies					
	203	11.8	1387	1.68	137

Absorption

The absolute bioavailability of riociguat is high (94%). Riociguat is rapidly absorbed with maximum concentrations (C_{max}) appearing 1 to 1.5 hours after tablet intake.

Intake with food does not affect riociguat AUC. C_{max} was reduced to a minor extent (35% lowering). Therefore, riociguat can be taken with or without food.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and α1-acidic glycoprotein being the main binding components.

Metabolism

N-demethylation, catalyzed by CYP1A1, CYP3A4, CYP3A5, and CYP2J2, is the major biotransformation pathway of riociguat leading to its major circulating active metabolite M1 (pharmacological activity:

1/10th to 1/3rd of riociguat) which is further metabolized to the pharmacologically inactive N-glucuronide.

CYP1A1 catalyzes the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, for instance, present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33 to 45%) and biliary/fecal routes (48 to 59%). Four to 19% of the administered dose is excreted as unchanged riociguat via the kidneys, and 9 to 44% of the administered dose is found as unchanged riociguat in feces.

Linearity / Non-linearity

Riociguat pharmacokinetics is linear from 0.5 to 2.5 mg.

In pulmonary hypertension patients, inter-individual variability (CV%) of riociguat exposure (AUC) across all doses is approximately 60%. The intra-individual variability is considerably lower with 35% for riociguat trough plasma concentration (C_{trough}).

Special Populations and Conditions

- **Geriatrics (≥65 years)**: exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 40% higher in elderly, mainly due to reduced (apparent) total and renal clearance (see 4 DOSAGE AND ADMINISTRATION).
- **Gender, Ethnicity, Weight Categories**

  Pharmacokinetic studies revealed no relevant differences due to gender, ethnicity or weight in the exposure to riociguat.
- **Hepatic Insufficiency:** There was no clinically relevant change in exposure in cirrhotic subjects with mild-hepatic impairment (classified as Child Pugh A).

  In cirrhotic subjects with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 50 to 70% compared to healthy controls (see 4 DOSAGE AND ADMINISTRATION, Hepatic Impairment).

  There are no data in patients with severe hepatic impairment (classified as Child Pugh C), and, therefore, the use of ADEMPAS is not recommended in these patients (see 7.1 Special Populations and 4 DOSAGE AND ADMINISTRATION, Hepatic Impairment).
- **Renal Insufficiency:** Overall, mean dose- and weight- normalized exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function. Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In individuals with mild (creatinine clearance 50 to 80 mL/min), moderate (creatinine clearance 30 to <50 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 43%, 104%, or 44%, respectively (see 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment).

There are no data in patients with creatinine clearance <15 mL/min or on dialysis. Therefore use is not recommended in patients with creatinine clearance <15 mL/min or on dialysis (see 7.1 Special Populations and 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment).

Due to the high plasma protein binding riociguat is not expected to be dialyzable.

11 STORAGE, STABILITY AND DISPOSAL

ADEMPAS should be stored at room temperature between 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for ADEMPAS.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

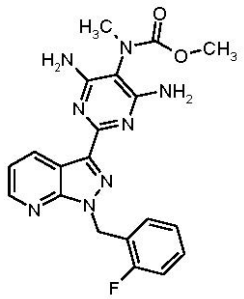
Proper name: Riociguat

Chemical name: Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate

Molecular formula: $C_{20}H_{19}FN_8O_2$

Molecular weight: 422.42

Structural formula:



Physicochemical properties: Riociguat is a white to yellowish, crystalline, non-hygroscopic substance. In solid form it is stable to temperature, light, and humidity.

The solubility at 25°C in water: 4 mg/L, in ethanol: 800 mg/L, in 0.1 M HCl (pH 1): 250 mg/L and in buffer (phosphate) pH 7: 3 mg/L. In the pH range of 2 to 4 the solubility showed strong pH-dependency. Solubility increases at lower pH values.

14 CLINICAL TRIALS

The ADEMPAS Phase III program included the CHEST-1 study in CTEPH patients, and the PATENT-1 study in patients with PAH.

14.1 Clinical Trials by Indication

Table 7: Summary of patient demographics for clinical trials

Study #	Study Design	Dosage, Route of administration and duration	Study subjects (n)	Mean Age (range)	Sex
Use in patients with chronic thromboembolic pulmonary hypertension (CTEPH)					
CHEST-1	Randomized, double-blind, multi-national,	Patients treated and valid for safety	261 patients	The patient population included male and female patients	Male and Female

Study #	Study Design	Dosage, Route of administration and duration	Study subjects (n)	Mean Age (range)	Sex
	multi-centre, placebo controlled Phase III study	randomized to one of two treatment groups: riociguat individual dose titration (IDT) up to 2.5 mg tid (n=173, referred to as the riociguat group), or placebo (n=88). During an 8-week titration phase, the dose of riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension. An individualized dose was reached at the end of the titration. At the end of the 16-week treatment phase, 77% of patients in the riociguat group were on the highest dose of 2.5 mg, 13% were on 2.0 mg and the remainder on lower doses.		between the ages of 19 and 80 (mean age: 59.3 years).	

Study #	Study Design	Dosage, Route of administration and duration	Study subjects (n)	Mean Age (range)	Sex
CHEST-2	Open-label extension trial	Patients previously randomized to either riociguat or placebo in CHEST-1 received individualized dose-titrated riociguat (capped at 2.5 mg tid)	237 patients who had completed CHEST-1	The patient population from CHEST-1 included male and female patients between the ages of 19 and 80 (mean age: 59.3 years).	Male and Female
Use in patients with pulmonary arterial hypertention (PAH)					
PATENT-1	Randomized, double-blind, multi-national, multi-centre, placebo controlled, phase III study	In PATENT-1, 443 patients with baseline 6MWD of 150 to 450 m, a PVR > 300 dyn*s*cm^{-5}, mean PAP >25 mmHg and systemic systolic pressure >95 and <180 mmHg were randomized to three groups in a 4 to 2 to 1 ratio to either: (1) and Individual Dose Titration (IDT) group on riociguat 1.0 to 2.5 mg tid (254 patients titrated by steps of 0.5 mg tid every two weeks), (2) placebo (126 patients), or (3) to a riociguat 1.0 to 1.5 mg tid dose group with dose capped at 1.5 mg tid (63 patients - *exploratory arm*, no statistical	443 patients	The overall patient population included male and female (79%) patients who were between the ages of 18 and 80 years (mean age: 51 years and approximately 25% ≥65 years)	Male and Female

Study #	Study Design	Dosage, Route of administration and duration	Study subjects (n)	Mean Age (range)	Sex
		testing performed).			
PATENT-2	open label extension study	Individual optimal doses of riociguat	396 patients who had completed PATENT-1	The overall patient population in PATENT-1 included male and female (79%) patients who were between the ages of 18 and 80 years (mean age: 51 years and approximately 25% ≥65 years)	Male and Female

CHEST-1 and CHEST-2 Study in patients with chronic thromboembolic pulmonary hypertension (CTEPH)

CHEST-1: This study was conducted in patients with inoperable, or persistent or recurrent CTEPH after surgical treatment. Patients were included who were inoperable (assessed by an independent adjudication committee or an experienced surgeon), or who had recurrent or persistent CTEPH after undergoing pulmonary endarterectomy (PEA).

72% of patients had inoperable CTEPH, 28% had recurrent or persistent CTEPH following PEA.

The majority of patients were classified as World Health Organization (WHO) Functional Class II (31%) or III (64%) at baseline. The mean baseline 6MWD was 347 m. All patients were treatment naïve (PAH-specific medication was excluded).

Eligible patients had the option to enter an open-label extension trial (CHEST-2), where all patients received an individualized optimal dose of riociguat.

PATENT-1 and PATENT-2 Study in patients with pulmonary arterial hypertension (PAH)

PATENT-1: This study (PATENT-1) was conducted in patients with PAH who were either treatment-naïve or pre-treated with an endothelin receptor antagonist (ERA) or a prostacyclin analogue (PCA) (inhaled, oral or subcutaneous).

The patient population had been diagnosed with either idiopathic PAH (61%), familial PAH (2%), PAH associated with connective tissue disease (25%), operated congenital heart disease (8%), portal hypertension (3%), or associated PAH due to anorexigen or amphetamine use (1%).

The majority of patients were classified as WHO Functional Class II (42%) or III (54%) at baseline. The overall mean baseline 6MWD was 363 m. 50% of patients were treatment naïve, 44% were pretreated with ERAs and 6% were pretreated with prostacyclin analogues alone.

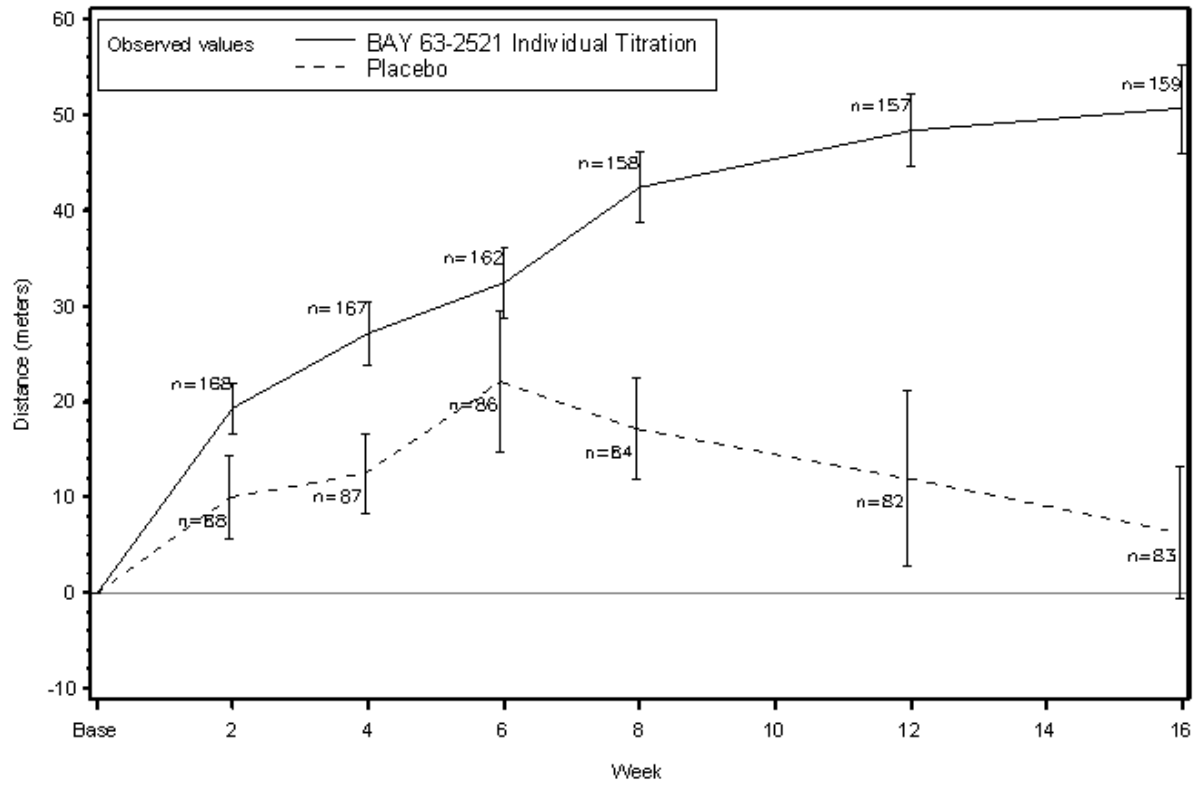
The 12-weeks treatment period included an 8-week titration phase, during which the dose of riociguat was titrated every 2 weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension, was followed by a 4-week treatment at the 'optimal' dose reached during the titration phase. At the end of the 12-week treatment phase, 75% of patients in the riociguat IDT group were on the highest dose of 2.5 mg, 15% were on 2.0 mg and the remainder on lower doses. Eligible patients of the three groups had the option to enter an open-label extension trial (PATENT-2), where all patients received individual optimal doses of riociguat.

CHEST-1 and CHEST-2 Study in patients with chronic thromboembolic pulmonary hypertension (CTEPH)

CHEST-1: Improvements in the primary efficacy variable, the six minute walk distance (6MWD), were apparent from week 2 onward, and at week 16 the increase in 6MWD within the riociguat group was 46 m (least-squares mean) (95% Confidence Interval (CI): 25 m to 67 m; p<0.0001) compared to placebo (ITT analysis, see Figure 1). Improvements of riociguat over placebo were observed in all sub-groups evaluated. Inoperable patients (n=189) demonstrated an increase in 6MWD of 54 m (29 m to 79 m), and patients with recurrent or persistent CTEPH following PEA (n=72) demonstrated an increase in 6MWD of 27 m (-10 m to 63 m). In patients with a WHO Functional Class of III/IV at baseline, riociguat led to a 53 m (27 m to 79 m) improvement in the 6MWD from baseline to week 16; in patients with a WHO Functional Class of I/II at baseline, the treatment effect was 26 m (-9 m to 59 m).

A larger proportion of patients in the riociguat group than in the placebo group had an improvement in 6MWD of at least 30 m by week 16: (63% vs. 30%) (see Figure 1).

Figure 1: Mean (± standard error) changes from baseline in the distance walked in 6 minutes (modified intention-to-treat population without imputation of missing values) during the 16 week of CHEST-1 study



Treatment with riociguat resulted in improvements across the secondary efficacy variables. There were significant reductions in PVR and NT-proBNP, and a significant improvement in WHO Functional Class of at least one Functional Class in the riociguat group at week 16 [last visit] of 33% vs. 15% in the placebo group, while a decline of at least one Functional Class was observed in 5% of patients in riociguat group vs. 7% in placebo group (p=0.0026) (see Table 8). There were also favorable effects in the riociguat group on time to clinical worsening, Borg CR 10 Scale, EQ-5D questionnaire, and LPH questionnaire (see Table 9).

Table 8: Effects of Riociguat on the Change in WHO Functional Class in CHEST-1 from Baseline to Week 16

Change in WHO Functional Class	Riociguat (n=173)	Placebo (n=87)
Improved	57 (33%)	13 (15%)
Stable	107 (62%)	68 (78%)
Deteriorated	9 (5%)	6 (7%)
	p-value=0.0026	

Table 9: Summary of Efficacy Results for Pre-defined Variables in the Hierarchical Testing Order - CHEST-1, ITT Analysis Set

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value
6MWD (m) (primary)	46	25 to 67	<0.0001*
PVR (dyn*s* cm^{-5})	-246	-303 to -190	<0.0001*
NT-proBNP (pg/mL)	-444	-843 to -45	<0.0001*
WHO Functional Class	32.9%[a] riociguat 14.9%[a] placebo	N/A	0.0026*
Time to clinical worsening[b]	2.3%[c] riociguat 5.7%[c] placebo	N/A	0.1724[d]
Borg CR 10 score	-0.8[e] riociguat 0.2[e] placebo	N/A	0.0035[f]
EQ-5D score	0.13	0.06 to 0.21	<0.0001
LPH score	-5.76	- 10.45 to -1.06	0.1220

Abbreviations: LS = least square; CI = confidence interval; IDT = individual dose titration (riociguat 1.0 to 2.5 mg); 6MWD = 6 minute walking distance; PVR = pulmonary vascular resistance; NT-proBNP = N-terminal prohormone brain natriuretic peptide; EQ-5D = European quality of life 5-dimensions instrument; LPH = Living with Pulmonary Hypertension

* Statistically significant

a Improvement by at least 1 WHO Functional Class in the respective treatment group

b Time to clinical worsening is defined as the number of days from start of study drug to the event of clinical worsening

c Percentage of subjects with one or more clinical worsening event in the respective treatment group

d Stratified log-rank test p-value for time to clinical worsening

e Change from baseline to last visit in the respective treatment group

f Due to the hierarchical testing strategy, formal statistical testing stopped at this point.

Invasive hemodynamic parameters were assessed in CHEST-1. Right heart catheterization was performed at the beginning and the end of the study period in 233 patients. A statistically significant reduction of PVR (-246 dyn*s*cm^{-5}, p<0.0001), mean pulmonary artery pressure (PAP_{mean}) (-5.0 mmHg, p<0.0001) and an increase in cardiac index (0.47 L/min/m^2; p<0.0001) was shown in the riociguat group compared to placebo (see Table 10).

Table 10: CHEST 1, Change in Hemodynamic Parameters from Baseline to Last Visit

Parameter (unit)	Mean change		LS mean difference	95% CI	Stratified Wilcoxon test p-value
	RIO	PBO			
PCWP (mmHg)	0.59	0.18	0.58	-0.36 to 1.53	0.2285
RAP (mmHg)	-1.04	-0.55	-0.55	-1.72 to 0.62	0.3593
PAPsyst (mmHg)	-6.84	0.95	-7.52	-10.88 to -4.16	<0.0001
PAPdiast (mmHg)	-3.05	0.67	-3.62	-5.30 to -1.95	0.0002
PAPmean (mmHg)	-4.31	0.76	-4.96	-6.75 to -3.16	<0.0001
MAP (mmHg)	-9.27	-0.29	-9.15	-11.83 to -6.46	<0.0001
SvO_2 (%)	2.95	-0.44	3.85	1.46 to 6.25	0.0010
CO (L/min)	0.81	-0.03	0.86	0.59 to 1.12	<0.0001
CI ($L/min/m^2$)	0.45	-0.01	0.47	0.33 to 0.62	<0.0001
PVR* ($dyn^*s^*cm^{-5}$)	-226	23.1	-246.43	-303.33 to -189.53	<0.0001
PVRI ($dyn^*s^*cm^{-5*}m^2$)	-397	48.3	-448.95	-553.62 to -344.27	<0.0001
SVR ($dyn^*s^*cm^{-5}$)	-445	16.6	-478.24	-602.30 to -354.19	<0.0001
SVRI ($dyn^*s^*cm^{-5*}m^2$)	-799	53.7	-914.16	-1140.97 to -687.35	<0.0001

Abbreviations: CI = Cardiac Index; CO = Cardiac Output; MAP = Mean Arterial Pressure; PAPdiast = Diastolic Pulmonary Arterial Pressure; PAPmean = Mean Pulmonary Arterial Pressure; PAPsyst = Systolic Pulmonary Arterial Pressure; PBO = Placebo; PCWP = Pulmonary Capillary Wedge Pressure; PVR = Pulmonary Vascular Resistance; PVRI = Pulmonary Vascular Resistance Index; RAP = Right Atrial Pressure; RIO = Riociguat 1.0-2.5 mg; SvO_2 = Venous Oxygen Saturation Rate; SVR = Systolic Vascular Resistance; SVRI = Systolic Vascular Resistance Index

* PVR was a secondary endpoint in the study

NT-proBNP levels were significantly reduced: placebo-corrected mean change from baseline was -444 pg/mL, CI -843 to -45, p<0.0001 (see Table 9).

A greater improvement in WHO Functional Class was observed in the riociguat IDT group than in the placebo group (see Table 9). A higher proportion of patients in the riociguat IDT group than in the placebo group had an improvement of at least one Functional Class (32.9% vs. 14.9%).

Time to clinical worsening (TTCW) was not statistically significantly different compared to placebo, but there was a trend in favour of the riociguat-treated patients (see Table 9). The secondary efficacy variable of TTCW was a combined endpoint of death (all-cause mortality), and events reflective of residual clinical worsening. Benefit was observed in both inoperable and operable CTEPH patients.

Patients previously randomized to either riociguat or placebo in CHEST-1 received individualized dose-titrated riociguat (capped at 2.5 mg tid) in an open-label extension study of CHEST-1.

CHEST-2: The open label extension study (CHEST-2) included 237 patients who had completed CHEST-1. At the cut-off date in the CHEST-2 study, the mean treatment duration total population was 1077 days (± 433). The probabilities of survival at 1, 2, and 3 years were 97%, 93%, and 89%, respectively. Without a control group, these data must be interpreted cautiously and cannot be used to determine the long-term effect of riociguat on mortality.

Patients on riociguat in CHEST-1 (n=129) ended the study with a 51.2 ± 61.8 m (mean±SD) improvement in 6MWD compared to baseline; in CHEST-2 improvement in 6MWD in the ricociguat group was 57.4 ± 69.0 m (n=155), 55.8 ± 62.5 m (n=138), and 51.0 ± 65.5m (n=128) at 12 weeks, 12 months and 24 months. Patients on placebo in CHEST-1 ended the study with a 4.1 ± 66.2 m (n=65) improvement in 6MWD compared to baseline; in CHEST-2 improvement in 6MWD in this former

placebo group was 43.0 ± 72.3 m (n=82), 45.3±70.8 m (n=71), 41.3±77.8 (n=65) 12 weeks, 12 months and 24 months. Improvements in 6MWD persisted at 2 years in CHEST-2. Mean change from baseline for the overall population (N=237) was 56.5 m at 6 months (n=218), 50.9 m at 9 months (n=219), 52.2 m at 12 months (n=209) and 47.8m at 24 months (n=193).

Of the patients on riociguat in CHEST-1, 34.9% completed that study with a ≥ 1 class improvement in WHO Functional Class, and 3.9% with a 1 class deterioration compared to baseline in CHEST-1: 34.9/3.9% (n=129). At 12 weeks and 24 months into CHEST-2, these improvement/deterioration fractions in the riociguat group were 40.7/3.2% (n=68) and 41.8%/2.2% (n=59), respectively. Of the patients on placebo in CHEST-1, 13.8% ended that study with a ≥ 1 class improvement in WHO Functional Class, and 3.1% with a 1 class deterioration compared to baseline in CHEST-1: 13.8%/3.1% (n=65). At 12 weeks and 24 months into CHEST-2 these improvement/deterioration fractions in the former placebo group were 39.5%/2.5% (n=34) and 34.3%/2.9% (n=26), respectively.

The probability of survival was 97% after 1 year and 93% after to 2 years of Adempas treatment. Without a control group, these data must be interpreted cautiously and cannot be used to determine the long-term effect of riociguat on mortality.

PATENT-1 and PATENT-2 Study in patients with pulmonary arterial hypertension (PAH)

PATENT-1: Treatment with riociguat IDT resulted in a statistically significant (p=<0.0001) improvement in 6MWD compared to placebo by a mean increase at 12 week of 36 m (95% CI 20, 52).

The pre-specified primary endpoint of the study was the change in 6MWD from baseline to week 12 and was based on imputed values. The imputation for missing values included last observed value, not including follow-up for patients who completed the study or withdrew. In case of death or clinical worsening without a termination visit or a measurement at that termination visit, the imputed worst value (zero) was used.

Results of the 6MWD over 12 weeks for the PATENT-1 study are shown in Figure 2.

Figure 2: PATENT-1 Mean Change from Baseline in the 6-Minute Walk Distance

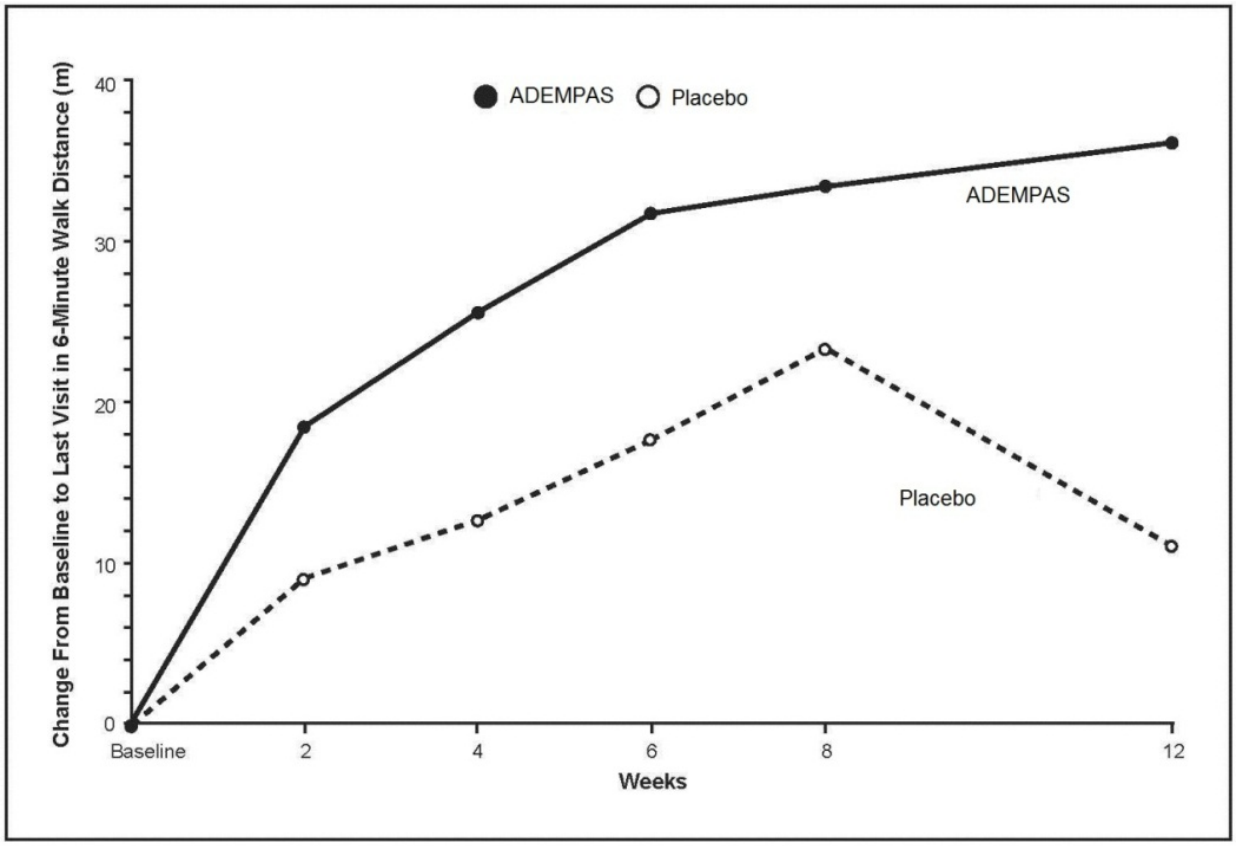
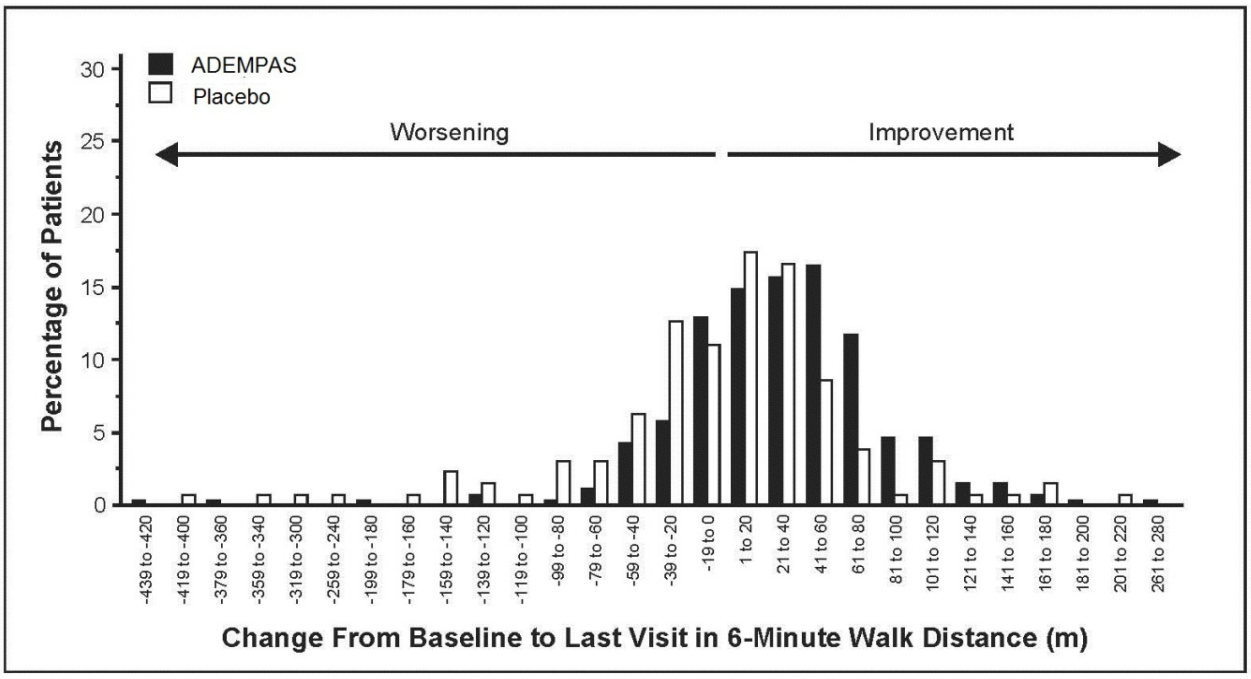


Figure 3 illustrates the results of the ADEMPAS and placebo treatment groups displayed as a histogram summarizing the treatment effect on the 6MWD. The patients are grouped by change in 20 meters from baseline. Overall this figure shows that patients treated with ADEMPAS benefit compared to those treated with placebo. As demonstrated in Figure 3, 193 patients receiving ADEMPAS (76%) experienced an improvement in 6MWD compared to 74 patients (59%) on placebo.

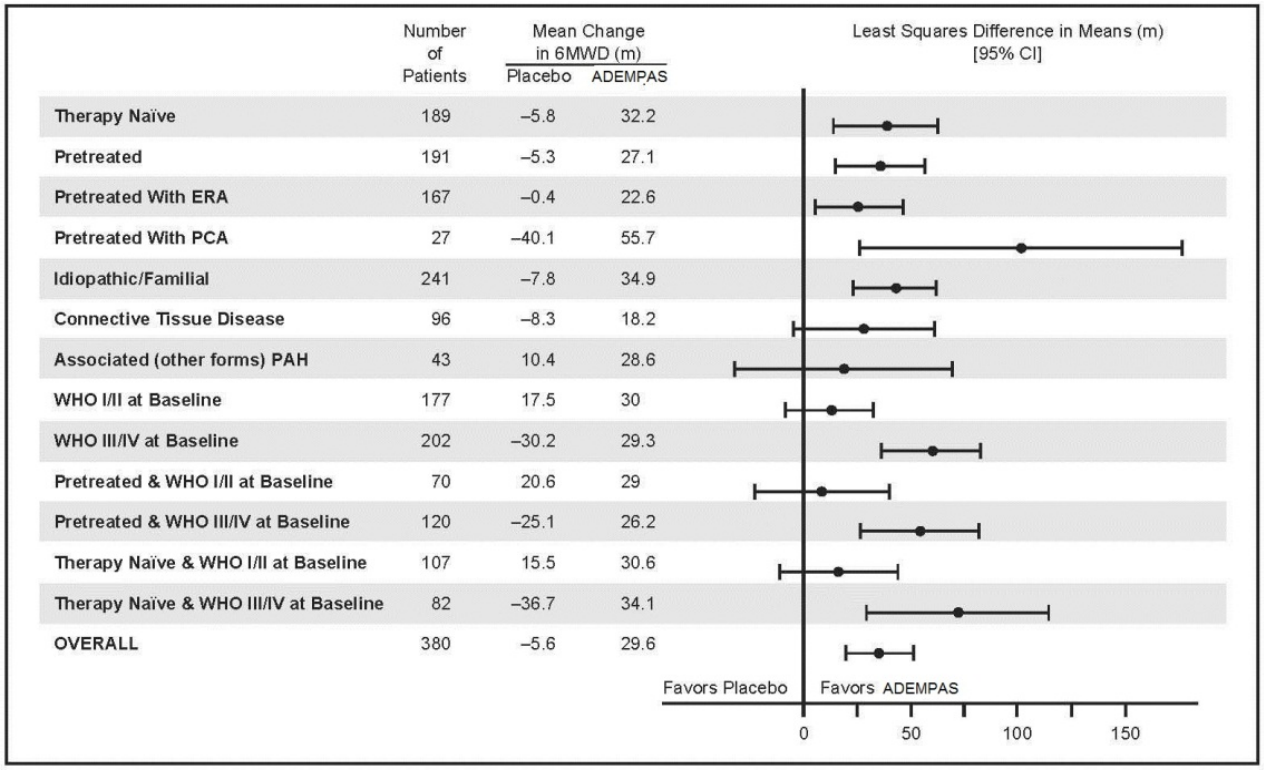
Figure 3: PATENT-1 Distribution of Patients by Change from Baseline in 6-Minute Walk Distance



Improvements 6MWD were apparent from Week 2 onward. At Week 12, the placebo-adjusted mean increase in 6MWD within the ADEMPAS group was 36 m (95% CI: 20 m to 52 m; p<0.0001). For PATENT-1, the median difference (Hodges-Lehmann non-parametric estimate) in 6MWD was 29 m (95% CI, 17 m to 40 m). There was an exploratory 1.5 mg capped titration arm (n = 63). The data did not suggest incremental benefit from escalating dose from 1.5 mg three times a day to 2.5 mg three times a day.

Placebo-adjusted changes in 6MWD at 12 weeks were evaluated in subgroups (see Figure 4).

Figure 4: PATENT-1 Mean Treatment Difference in Change from Baseline to Last Visit in 6-Minute Walk Distance (meter) by Prespecified Subgroups



WHO Functional Class improvements in the IDT (individual dose titration) arm of the PATENT-1 trial are shown in Table 11.

Table 11: Effects of ADEMPAS on the Change in WHO Functional Class in PATENT-1 from Baseline to Week 12

Change in WHO Functional Class	ADEMPAS (IDT) (n=254)	Placebo (n=125)
Improved	53 (21%)	18 (14%)
Stable	192 (76%)	89 (71%)
Deteriorated	9 (4%)	18 (14%)
	p-value = 0.0033	

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.

Effects of ADEMPAS in PATENT-1 on events of clinical worsening are shown in Table 12.

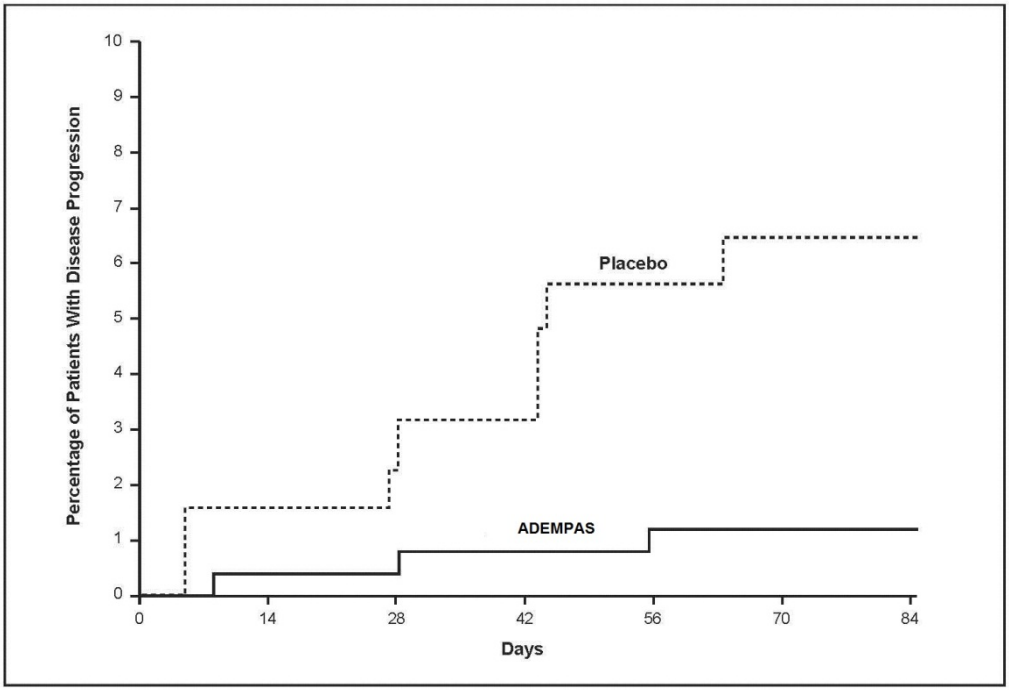
Table 12: Effects of ADEMPAS in PATENT-1 on Events of Clinical Worsening (ITT analysis set)

Clinical Worsening Events	ADEMPAS (IDT) (n=254)	Placebo (n=126)
Patients with any clinical worsening*	3 (1.2%)	8 (6.3%)
Death	2 (0.8%)	3 (2.4%)
Hospitalizations due to PH	1 (0.4%)	4 (3.2%)
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)
Persistent worsening of FC due to PAH	0	1 (0.8%)
Start of new PAH treatment	1 (0.4%)	5 (4.0%)

* p-value=0.0285 (Mantel-Haenszel estimate)
Note: Patients may have had more than one event of clinical worsening

ADEMPAS-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p=0.0046; Stratified log-rank test). Significantly fewer events of clinical worsening up to week 12 (last visit) were observed in patients treated with ADEMPAS (1.2%) compared to placebo (6.3%) (p=0.0285, Mantel-Haenszel estimate). The Kaplan-Meier plot of time to clinical worsening is presented in Figure 5.

Figure 5: PATENT-1 Time (in Days) to Clinical Worsening (ITT analysis set)



In the PATENT-1 study riociguat demonstrated a statistically significant reduction of NT-proBNP, placebo-corrected mean change from baseline: -432 ng/L, 95% CI -782 to -82 and Borg CR 10 scale, change from baseline to last visit in the respective treatment group: -0.4 riociguat vs 0.1 placebo.

Invasive hemodynamic parameters were assessed in PATENT-1 and are shown in Table 13. Right heart catheterization was performed at the beginning and the end of the study period in 339 patients.

Table 13: PATENT-1 Change in Hemodynamic Parameters from Baseline to Last Visit: Comparison of Riociguat IDT and Placebo

Parameter (unit)	Mean change		LS mean[a] difference	95% CI	Stratified[b] Wilcoxon test p-value
	RIO	PBO			
PCWP (mmHg)	1.08	0.46	0.41	-0.36 to 1.18	0.0830
RAP (mmHg)	-0.20	0.97	-1.01	-2.15 to 0.13	0.0734
PAPsyst (mmHg)	-5.39	0.78	-6.73	-9.43 to -4.04	<0.0001
PAPdiast (mmHg)	-3.19	-1.12	-2.41	-4.15 to -0.68	0.0110
PAPmean (mmHg)	-3.93	-0.50	-3.83	-5.61 to -2.06	0.0002
MAP (mmHg)	-8.54	-1.40	-7.25	-9.60 to -4.90	<0.0001
SvO_2 (%)	3.15	-2.33	5.02	3.20 to 6.84	<0.0001
CO (L/min)	0.93	-0.01	0.93	0.70 to 1.15	<0.0001
CI ($L/min/m^2$)	0.54	-0.02	0.56	0.44 to 0.69	<0.0001
PVR ($dyn*s*cm^{-5}$)	-223	-8.9	-225.72	-281.37 to -170.08	<0.0001
PVRI ($dyn*s*cm^{-5}*m^2$)	-374	-22.4	-376.81	-468.90 to -284.72	<0.0001
SVR ($dyn*s*cm^{-5}$)	-448	-67.5	-394.57	-472.95 to -316.19	<0.0001
SVRI ($dyn*s*cm^{-5}*m^2$)	-753	-130	-675.31	-800.84 to -549.79	<0.0001

Abbreviations: CI = Cardiac Index; CO = Cardiac Output; MAP = Mean Arterial Pressure; PAPdiast = Diastolic Pulmonary Arterial Pressure; PAPmean = Mean Pulmonary Arterial Pressure; PAPsyst = Systolic Pulmonary Arterial Pressure; PBO = Placebo; PCWP = Pulmonary Capillary Wedge Pressure; PVR = Pulmonary Vascular Resistance; PVRI = Pulmonary Vascular Resistance Index; RAP = Right Atrial Pressure; RIO = Riociguat 1.0-2.5 mg; SvO_2 = Venous Oxygen Saturation Rate; SVR = Systolic Vascular Resistance; SVRI = Systolic Vascular Resistance Index

a Last visit = Last observed value post-baseline (not including follow-up)

b Stratified Wilcoxon test by region and stratification group

PATENT-2: An open label extension study (PATENT-2) included 396 patients who had completed PATENT-1. At the cut-off date in the PATENT-2 study, the mean treatment duration total population was 1146 days (± 479). The probabilities of survival at 1, 2, and 3 years were 97%, 93%, and 88%, respectively. Without a control group, these data must be interpreted cautiously and cannot be used to determine the long-term effect of riociguat on mortality.

The long-term 6MWD data indicate maintenance of the riociguat treatment effect, with improvement in 6MWD observed for at least 18 months. Mean change from baseline in PATENT-2 for the total group (N=396) was 50.2 ± 65.5 m at 12 weeks (n=396), 50.2 ± 72.6 m at 12 months (n=351) and 46.1 ± 83.0 m at 24 months (n=316).

The findings for 6MWD, NT-proBNP, WHO Functional Class and Borg CR 10 Scale in study PATENT-2 were maintained and consistent with the key findings seen in study PATENT-1.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Non-clinical data revealed no unusual hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, and carcinogenicity. Embryo-fetal toxicity, including malformations, was seen in developmental/reproductive studies.

Repeated Dose Toxicity

Effects observed in repeat-dose toxicity studies were mainly due to the pharmacodynamic activity of riociguat (hemodynamic and smooth muscle relaxing effects), and occurred at systemic exposures comparable to or less than that at the maximum human recommended dose (MRHD).

In rats, these included: clinical signs such as penile erection likely due to vasodilation; increased water consumption and urine volume and consequently decreased urine density and concentrations of constituents, increased adrenal gland weight and width of the zona glomerulosa; prominent/dilated vascular spaces in wall of mesenteric veins; increased red blood cell parameters and reticulocyte counts; and intestinal effects (distended abdomen, increased girth, elongated intestines, dilated cecum) presumed due to reduced gastrointestinal motility.

Bile duct activation and/or hyperplasia and increased periportal inflammatory infiltration was seen in rats given 100 g/kg/day in a 13-week study resulting exposures about 7 times that at the MRHD, although the incidence of biliary cysts was increased in high dose males rats in the carcinogenicity study at exposures only slightly above that at the MRHD. Similar findings were not seen in mice or dogs.

Increased heart weight at therapeutic exposures was without microscopic correlate in subchronic and chronic rat studies. However, cardiac enlargement and increased incidences of atrial thrombus, dilation, cardiomyopathy, and vasculopathy in high dose males in the rat carcinogenicity study occurred at exposures more than twice that at the MRHD, although exposure was less than that at the MRHD at the no-effect dose.

Clinical effects in dogs were mainly referable to the gastrointestinal system, and included vomiting, diarrhea, decreased food consumption, and weight loss.

In dogs, marked decreases in systolic and diastolic blood pressure and compensatory increases in heart rate that occurred at ≥ 0.3 mg/kg/day were without a no effect dose level. Pathologic lesions in heart (myocardial degeneration, myocardial fibrosis of papillary muscle, endocarditis) and in coronary vessels (vascular/perivascular edema, vascular hypertrophy) also occurred at ≥ 0.3 mg/kg/day. Hemodynamic and cardiovascular hemodynamic changes occurred in dogs at systemic exposures comparable to or less than exposure at the MRHD.

Carcinogenicity:

Neither riociguat nor its major circulating active metabolite was genotoxic, both being negative in bacterial mutation (Ames) assays, *in vitro* chromosome aberration assays in Chinese Hamster V79 cells, and *in vivo* bone marrow micronucleus studies in male mice. Riociguat was also negative in an *in vivo* bone marrow cytogenetic study conducted in male mice.

Genotoxicity:

Neither riociguat nor its major circulating active metabolite was genotoxic, both being negative in bacterial mutation (Ames) assays, *in vitro* chromosome aberration assays in Chinese Hamster V79 cells, and *in vivo* bone marrow micronucleus studies in male mice. Riociguat was also negative in an *in vivo* bone marrow cytogenetic study conducted in male mice.

Reproductive and Developmental Toxicology:

Studies in rats and rabbits have shown marked reproductive toxicity of riociguat and its main metabolite.

Administration of riociguat to rats in the pre- and postnatal period resulted in a decreased live birth index and decreased survival up to day 4 post-partum. At the no-observed-adverse-effect level (NOAEL) for the effects, the rat systemic exposure to riociguat was lower than the maximum human exposure. Administration of riociguat to rats during the gestation period resulted in an increased rate of cardiac malformations and an increase in post-implantation loss, including early resorption. At the NOAEL for these effects, the rat systemic exposure to riociguat was in the range of the maximum human exposure. The major fetal effects of the main metabolite (M1) of riociguat, administered to rats during the gestation period included: a decrease in fetal weight, an increased incidence of underdeveloped or missing thyroid glands, and retarded ossification. At the NOAEL for these effects, the rat systemic exposure to M1 was comparable to the maximum human exposure.

In rabbits, abortion and fetal toxicity were seen with riociguat administered during the gestation period starting at systemic exposure lower than the maximum human exposure. Also in rabbits, abortion and total resorption were seen with M1 administered during the gestation period. At the NOAEL for these effects, the rabbit systemic exposure to M1 was lower than the maximum human exposure.

In rats, no effects on male and female fertility were seen with riociguat, but its main metabolite (M1) produced a slight decrease in implantation rate at systemic exposure comparable to maximum human exposure.

Bone Toxicity

In fast growing, adolescent rats, effects on bone formation (i.e., an increase in overall bone mass) were seen. In adult rats, when treatment was initiated during adolescence, increased bone remodeling/hyperostosis in the femur was observed in the 26-week chronic toxicity study at steady state systemic exposures in the range of human therapeutic levels. No bone effects were seen when treatment was initiated in adult, full grown rats.

Animal Pharmacology

In all species tested, the toxicological profile of ADEMPAS was characterized by effects secondary to the pharmacological mode of action – stimulation of the soluble guanylate cyclase and subsequent increase of intracellular cGMP levels. The cardiovascular, the gastrointestinal and the skeletal system were shown to be most sensitive to these effects.

Nonclinical safety testing of ADEMPAS revealed no toxicity of specific concern like hepatotoxicity and renal toxicity. Studies addressing the risk for QT-prolongation *in vitro* showed no relevant intrinsic effect of ADEMPAS on cardiac repolarization. The QT interval was not considered as affected when corrected for heart rate in conscious or anesthetized dogs after single oral administration of ADEMPAS or its main metabolite M1.

Human Pharmacology

ADEMPAS is a stimulator of soluble guanylate cyclase (sGC), an enzyme found in most mammalian cells including those of the cardiopulmonary system. sGC is also the receptor for nitric oxide (NO).

Pharmacodynamics

When NO binds to sGC, the enzyme catalyzes the synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intra-cellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation.

Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of nitric oxide, and insufficient stimulation of the NO-sGC-cGMP pathway.

Riociguat has a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.

Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

There is a direct relationship between riociguat plasma concentration and hemodynamic parameters such as systemic and pulmonary vascular resistance, systolic blood pressure, and cardiac output.

Pharmacokinetics

Absorption and Bioavailability

The absolute bioavailability of riociguat is high (94%). Riociguat is rapidly absorbed with maximum concentrations (C_{max}) appearing 1 to 1.5 hours after tablet intake.

Intake with food does not affect riociguat AUC. C_{max} was reduced to a minor extent (35% lowering). Therefore, riociguat can be taken with or without food.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and α1-acidic glycoprotein being the main binding components.

The volume of distribution is moderate with volume of distribution at steady state being approximately 30 L.

Metabolism

N-demethylation, catalyzed by CYP1A1, CYP3A4, CYP3A5, and CYP2J2, is the major biotransformation pathway of riociguat leading to its major circulating active metabolite M1 (pharmacological activity: $1/10^{th}$ to $1/3^{rd}$ of riociguat) which is further metabolized to the pharmacologically inactive N-glucuronide.

In vitro, ketoconazole, classified as a strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a 'multipathway CYP and P-gp/breast cancer resistance protein (BCRP) inhibitor' for riociguat metabolism and excretion.

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 most effectively catalyzed formation of riociguat main metabolite. The class of tyrosine kinase inhibitors was identified as potent inhibitors of CYP1A1, with erlotinib and gefitinib exhibiting the highest inhibitory potency *in vitro*. Therefore, drug-drug interactions by inhibition of CYP1A1 could result in increased riociguat exposure, especially in smokers. Therefore, strong CYP1A1 inhibitors should be used with caution.

Excretion

Total riociguat (parent compound and metabolites) is excreted via both renal (33 to 45%) and biliary/fecal routes (48 to 59%). Four to 19% of the administered dose is excreted as unchanged riociguat via the kidneys, and 9 to 44% of the administered dose is found as unchanged riociguat in feces.

Based on *in vitro* data riociguat and its main metabolite are substrates of the transporter proteins P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein).

With a systemic clearance of about 3 to 6 L/h, riociguat can be classified as a low-clearance drug. Elimination half-life is about 7 hours in healthy subjects and about 13 hours in patients.

Linearity / Non-linearity

Riociguat pharmacokinetics is linear from 0.5 to 2.5 mg.

Inter-individual variability (CV%) of riociguat exposure (AUC) across all doses is approximately 60%. The intra-individual variability is considerably lower with 35% for riociguat trough plasma concentration (C_{trough}).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrADEMPAS®

Riociguat Tablets

Read this carefully before you start taking **ADEMPAS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ADEMPAS**.

What is ADEMPAS used for?

ADEMPAS is used to treat pulmonary hypertension (high blood pressure in the lungs) in adults with the following conditions:

- pulmonary arterial hypertension (PAH; WHO Group 1). It can be taken on its own or with other PAH medications as prescribed by your health care provider.
- chronic thromboembolic pulmonary hypertension (CTEPH; WHO Group 4) when CTEPH cannot be resolved with an surgery, or if CTEPH is persistent or reoccurring after surgery.

How does ADEMPAS work?

ADEMPAS belongs to a class of medicines called soluble guanylate cyclase (sGC) stimulators. It works by stimulating an enzyme (sGC) in the blood vessels in the lungs, causing the blood vessels to relax and widen. This helps to lower the blood pressure in the lungs and improve the symptoms of pulmonary hypertension.

What are the ingredients in ADEMPAS?

Medicinal ingredient: Riociguat.

Non-medicinal ingredients: Cellulose microcrystalline, crospovidone, hydroxypropylcellulose, hypromellose 3cP, hypromellose 5cP, lactose monohydrate, magnesium stearate, sodium laurilsulphate, propylene glycol, and titanium dioxide.

In addition, the following tablet strengths also include other non-medicinal ingredients:

- 1 mg and 1.5 mg: Ferric oxide yellow.
- 2 mg and 2.5 mg: Ferric oxide red and ferric oxide yellow.

ADEMPAS comes in the following dosage forms:

Film-coated tablets: 0.5 mg (white), 1 mg (pale yellow), 1.5 mg (yellow-orange), 2 mg (pale orange), and 2.5 mg (red-orange) of riociguat.

Do not use ADEMPAS if:

- you are allergic to riociguat or any of the other ingredients in ADEMPAS.
- you are pregnant or planning to become pregnant.
- you are breast-feeding or planning to breast-feed.
- you are taking any of the following medicines:
  - sildenafil (e.g., VIAGRA or REVATIO), tadalafil (e.g., CIALIS or ADCIRCA), or vardenafil (e.g., LEVITRA and STAXYN) used to treat high blood pressure or erectile dysfunction.

- nitrates or nitric oxide donors (e.g., amyl nitrite) used to treat high blood pressure of coronary artery disease (CAD; a heart condition involving the heart arteries that do not supply enough blood, oxygen and nutrients to the heart).
- other sGC stimulators used to treat heart failure and PAH.

These are the common uses for each medicine. If you are unsure if you are taking these medicines, ask your healthcare professional.

- you have high blood pressure in your lungs associated with scarring of the lungs from an unknown cause (idiopathic interstitial pneumonias).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADEMPAS. Talk about any health conditions or problems you may have, including if you:

- are at a higher risk of bleeding. This can include if you:
  - are receiving treatment or medicines used to prevent blood clots (anticoagulants).
  - have a history of coughing up blood from the lungs (hemoptysis).
  - have previously undergone a procedure called bronchial arterial embolization to stop coughing up blood from the lungs.
- are receiving or plan to receive dialysis treatment.
- have experienced a sudden drop in blood pressure when you stand from a sitting position or when you stand after lying down.
- have heart or circulation problems.
- have kidney problems.
- have liver problems.
- have low blood pressure.
- have low fluid levels in your body (hypovolemia).
- have lung or breathing problems.
- have problems affecting your autonomic nervous system (ANS), which controls the automatic functions of the body.
- have problems digesting certain sugars (e.g., lactose intolerance). ADEMPAS contains lactose, a milk sugar.
- smoke cigarettes. You should not smoke during your treatment with ADEMPAS. Tell your healthcare professional, if you plan to stop or start smoking cigarettes during treatment.

Other warnings you should know about:

Driving and using machines: ADEMPAS can cause dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to ADEMPAS.

Pregnancy: Do not take ADEMPAS if you are pregnant. If there is a chance you could become pregnant, use reliable forms of birth control while you are taking ADEMPAS. If you are unsure about your birth control options, talk to your healthcare professional. Tell your healthcare professional right away if you become pregnant while taking ADEMPAS.

Testing and check-ups: Your healthcare professional will monitor your health throughout your treatment. They may do this by performing certain tests before and regularly during your treatment. This can include specific tests to monitor your blood pressure and risk of bleeding. If you notice any unexpected or excessive bleeding, tell your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Serious drug interactions with ADEMPAS include:

- sildenafil (e.g., VIAGRA or REVATIO), tadalafil (e.g., CIALIS or ADCIRCA), or vardenafil (e.g., LEVITRA and STAXYN), medicines used to treat high blood pressure or erectile dysfunction. Before taking ADEMPAS, you must stop taking sildenafil for at least 24 hours and tadalafil for at least 48 hours.
- nitrates or nitric oxide donors, medicines used to treat high blood pressure of coronary artery disease (CAD; a heart condition involving the heart arteries that do not supply enough blood, oxygen and nutrients to the heart).
- other sGC stimulators, medicines used to treat heart failure and PAH.

Do **not** take ADEMPAS if you are taking any of these medicines. Ask your healthcare professional if you are unsure.

The following may interact with ADEMPAS:

- antacids, medicines used to treat indigestion, heart burn, and upset stomach (e.g., aluminum hydroxide and magnesium hydroxide). Antacids should be taken at least 1 hour after ADEMPAS.
- antiepileptics, medicines used to control seizures or fits (e.g., phenytoin, carbamazepine, and phenobarbitone).
- antifungals, medicines used to treat fungal infections (e.g., ketoconazole, clotrimazole, miconazole, and itraconazole).
- carvedilol, a medicine used to treat heart failure and high blood pressure.
- cigarette smoking.
- cyclosporine, a medicine used to prevent rejection of transplanted organs.
- erlotinib (e.g., TARCEVA) or gefitinib (e.g., IRESSA), medicines used to treat cancer.
- granisetron, a medicine used to treat nausea and vomiting.
- medicines that can increase the pH of the upper gastrointestinal tract. Ask your healthcare professional if you are unsure.
- medicines used to treat human immunodeficiency virus (HIV) infection (e.g., abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, indinavir, lamivudine, rilpivirine, ritonavir, saquinavir, and tenofovir).
- niflumic acid, a medicine used to treat joints and muscular pain and inflammation.
- quinidine, a medicine used to treat irregular heart rhythm and malaria.
- St. John´s Wort, a herbal treatment for depression.
- tyrosine kinase inhibitors, medicines used to prevent the rejection of transplanted organs (e.g., imatinib, sorafenib and sunitinib).

These are the common uses for each medicine. If you are unsure if you are taking these medicines, ask your healthcare professional

How to take ADEMPAS:

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

- Treatment should only be initiated and monitored by a healthcare professional experienced in the treatment of CTEPH or PAH.
- ADEMPAS can be taken with or without food.

Usual dose:

Your healthcare professional will determine the right dose for you. This may depend on your age, condition, health, and how you respond to ADEMPAS.

The usual starting dose is 1 mg three times a day (approximately every 6 to 8 hours apart) for 2 weeks. Your healthcare professional may increase your dose every 2 weeks to a maximum of 2.5 mg three times a day (total of 7.5 mg a day).

Overdose:

If you think you, or a person you are caring for, have taken too much ADEMPAS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of ADEMPAS, skip the missed dose and take the next dose as scheduled. Do **not** double the dose to make up for the missed dose.

If you miss or forget to take ADEMPAS for 3 days or more, tell your healthcare professional. Your healthcare professional may need to adjust your dose.

What are possible side effects from using ADEMPAS?

These are not all the possible side effects you may have when taking ADEMPAS. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of ADEMPAS may include:

- abdominal pain or discomfort;
- abdominal swelling or bloating;
- constipation;
- diarrhea;
- dizziness;
- headache;
- indigestion
- nasal congestion;
- nausea;
- vomiting.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Bleeding events: nose bleeds, bleeding from the lungs, or coughing up blood.		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		✓	
Peripheral edema (swelling of the arms, hands, legs, or feet).	✓		
COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Dysphagia (difficulty swallowing): coughing or choking while eating or drinking, pain while swallowing, unable to swallow, drooling, hoarseness, regurgitating, heartburn, food or stomach acid backing up into the throat, or weight loss.		✓	
Gastritis (inflammation of the lining of the stomach): nausea, vomiting, feeling full in the upper abdomen after eating, or pain or burning in the upper abdomen that may get worse or better with eating.		✓	
Gastroenteritis (inflammation of the stomach and intestines): abdominal pain, diarrhea, nausea, or vomiting.	✓		
Gastroesophageal reflux disease (GERD) (stomach acid repeatedly flows back into the throat): heartburn after eating and might get worse at night or while lying down, regurgitating food or sour liquid, upper abdominal pain, chest		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
pain, difficulty swallowing, sensation of a lump in your throat, cough, or inflammation of the vocal cords.			
Palpitations: heart is skipping beats, beating too fast, pounding, or fluttering rapidly.		✓	
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store **ADEMPAS** at room temperature between 15°C and 30°C. Do not use after the expiry date stated on the label.

Keep out of reach and sight of children.

If you want more information about ADEMPAS:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's http://www.bayer.ca, or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

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