PRODUCT MONOGRAPH

PrADEMPAS®

riociguat (film-coated) tablet

0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg

Professed standard

Soluble Guanylate Cyclase (sGC) Stimulator

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PrADEMPAS®

riociguat

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form, Strength	Nonmedicinal Ingredients
Oral	Film-coated tablet, 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg	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 This is a complete listing.

INDICATIONS AND CLINICAL USE

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.

Pediatrics (<18 years of age)

Safety and effectiveness in pediatric patients have not been established (see WARNINGS AND PRECAUTIONS, Special Populations - Pediatrics).

Geriatrics (≥ 65 years of age)

Safety and effectiveness in geriatric patients up to 80 years of age have been established (see WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics).

CONTRAINDICATIONS

- Concomitant use of ADEMPAS (riociguat) 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 DRUG INTERACTIONS**,** Drug-Drug Interactions.)

- ADEMPAS is contraindicated during pregnancy and nursing (see WARNINGS AND PRECAUTIONS, Special Populations - Nursing Women and TOXICOLOGY**,** Reproductive Toxicology).
- Hypersensitivity to ADEMPAS or to any ingredient in the formulation (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- ADEMPAS is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

WARNINGS AND PRECAUTIONS

Hypotension

As a sGC stimulator, ADEMPAS (riociguat) acts as a vasodilator, lowering both pulmonary and systemic blood pressure. The demonstrated risk of hypotension should be carefully considered (see 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, severe left ventricular outflow obstruction or autonomic dysfunction as well as in patients on antihypertensive therapy or with resting hypotension.

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 CONTRAINDICATIONS).

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.

Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of ADEMPAS (riociguat) 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.

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) is not recommended, due to the pronounced increase in riociguat exposure (see DRUG INTERACTIONS**,** Drug-Drug Interactions).

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 DRUG INTERACTIONS**,** 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.

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

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. Thus, ADEMPAS is currently not indicated for use in patients < 18 years of age.

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.

Pregnancy/Fertility

There are no adequate data from the use of ADEMPAS in pregnant women. Studies in animals have shown reproductive toxicity (see TOXICOLOGY, Reproductive Toxicology). Therefore, ADEMPAS is contraindicated in females who are or may become pregnant (see 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 TOXICOLOGY, Reproductive Toxicology).

Nursing Women

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 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.

Effect of Cigarette Smoking

In cigarette smokers, riociguat exposure is reduced by 50 to 60% (see ACTION AND CLINICAL PHARMACOLOGY, 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 DOSAGE AND ADMINISTRATION, Smoking Status).

Effects on Ability to Drive or Use Machines

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.

ADVERSE REACTIONS

Adverse Drug 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 WARNINGS AND PRECAUTIONS, Bleeding).

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 PART II: SCIENTIFIC INFORMATION, 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).

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

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)
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	17.3	15.0
Edema peripheral		

Less Common Clinical Trial Adverse Drug Reactions

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

Abnormal Hematologic and Clinical Chemistry Findings

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.

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 (riociguat) 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 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.

Drug-Drug Interactions

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 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 CONTRAINDICATIONS).
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).	Concomitant use with strong multi-pathway CYP and P-gp/BCRP inhibitors, such as antifungal agents (eg, ketoconazole, itraconazole) is not recommended (see WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Metabolism)

Table 5: Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
HIV protease inhibitors - Ritonavir - Saquinavir	I	*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).	Concomitant use with strong multi-pathway CYP and P-gp/BCRP inhibitors, such as HIV protease inhibitors (eg, ritonavir) is not recommended
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 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.
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 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 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 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.

Table 5: Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
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 DOSAGE AND ADMINISTRATION).	Antacids should be taken at least 1 hour after ADEMPAS.
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.

Table 5: Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
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: $1/10^{th}$ to $1/3^{rd}$ 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)

Drug-Food Interactions

No clinically relevant interaction with food was observed (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Lifestyle Interactions

In cigarette smokers riociguat exposure is reduced by 50 to 60% (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Metabolism). Therefore patients are advised to stop smoking (see DOSAGE AND ADMINISTRATION, Smoking Status). Dose adjustment of ADEMPAS may be required in patients who stop or start smoking during treatment.

DOSAGE AND ADMINISTRATION

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.

Recommended Dose and Dosage Adjustment

Treatment Initiation

The recommended starting dose of ADEMPAS (riociguat) 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 tid, 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 (riociguat) is 7.5 mg.

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

Missed Dose

If a dose is missed, treatment should be continued with the next dose as planned.

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.

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Special Populations and Conditions**:** Geriatrics).

Pediatrics

ADEMPAS is not recommended for use in pediatrics.

Hepatic Impairment

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

ADEMPAS is not recommended in patients with severe hepatic impairment (Child Pugh C) (see WARNINGS AND PRECAUTIONS**,** 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics – Special Populations and Conditions**:** *Renal Insufficiency*).

ADEMPAS is not recommended in patients with creatinine clearance <15 mL/min or on dialysis (see WARNINGS AND PRECAUTIONS**,** 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 DRUG INTERACTIONS, Overview and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - *Metabolism*).

Concomitant Use with Antacids

Antacids should be taken at least 1 hour after ADEMPAS (see DRUG INTERACTIONS, Drug-Drug Interactions).

Strong CYP and P-gp/BCRP inhibitors

Consider a starting dose of 0.5 mg, three times a day when initiating ADEMPAS in patients receiving strong multipathway cytochrome P450 (CYP) and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (for example, ritonavir). Monitor for signs and symptoms of hypotension on initiation and on treatment with strong multipathway CYP and P-gp/BCRP inhibitors (see WARNINGS AND PRECAUTIONS, Concomitant Use with CYP or P-gp/BCRP Inhibitors and DRUG INTERACTIONS).

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 (riociguat) between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see ADVERSE REACTIONS).

No specific antidote is available.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ADEMPAS (riociguat) 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).

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.

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: $1/10^{th}$ to $1/3^{rd}$ 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.

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.

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

Elderly patients (≥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 DOSAGE AND ADMINISTRATION, Geriatrics (≥65 years of age)).

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 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 WARNINGS AND PRECAUTIONS, Special Populations and 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 DOSAGE AND ADMINISTRATION, 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 WARNINGS AND PRECAUTIONS, Special Population and DOSAGE AND ADMINISTRATION, Renal Impairment).

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

Gender, Ethnicity, Weight Categories

Pharmacokinetic studies revealed no relevant differences due to gender, ethnicity or weight in the exposure to riociguat.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for ADEMPAS (riociguat).

DOSAGE FORMS, COMPOSITION AND PACKAGING[1]

ADEMPAS (riociguat) is available as 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for oral administration containing the following inactive ingredients: cellulose microcrystalline, crospovidone, hypromellose 5cP, lactose monohydrate, magnesium stearate, sodium laurilsulphate. The film-coating contains the following inactive ingredients hydroxypropylcellulose, hypromellose 3cP, propylene glycol, titanium dioxide. ADEMPAS 1 mg, 1.5 mg, 2 mg and 2.5 mg tablets contain in addition ferric oxide yellow and ADEMPAS 2 mg and 2.5 mg tablets contain in addition ferric oxide red.

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.

[1] Not all presentations may be available in Canada.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

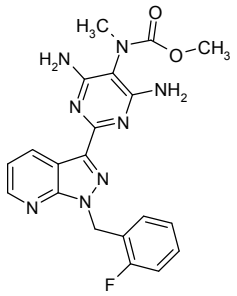
Proper name: Riociguat

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.

CLINICAL TRIALS

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

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

Study Design and Demographics

This randomized, double-blind, multi-national, multi-centre, placebo controlled Phase III 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).

The patient population included male and female patients between the ages of 19 and 80 (mean age: 59.3 years). 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).

CHEST-1 included 261 patients treated and valid for safety 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.

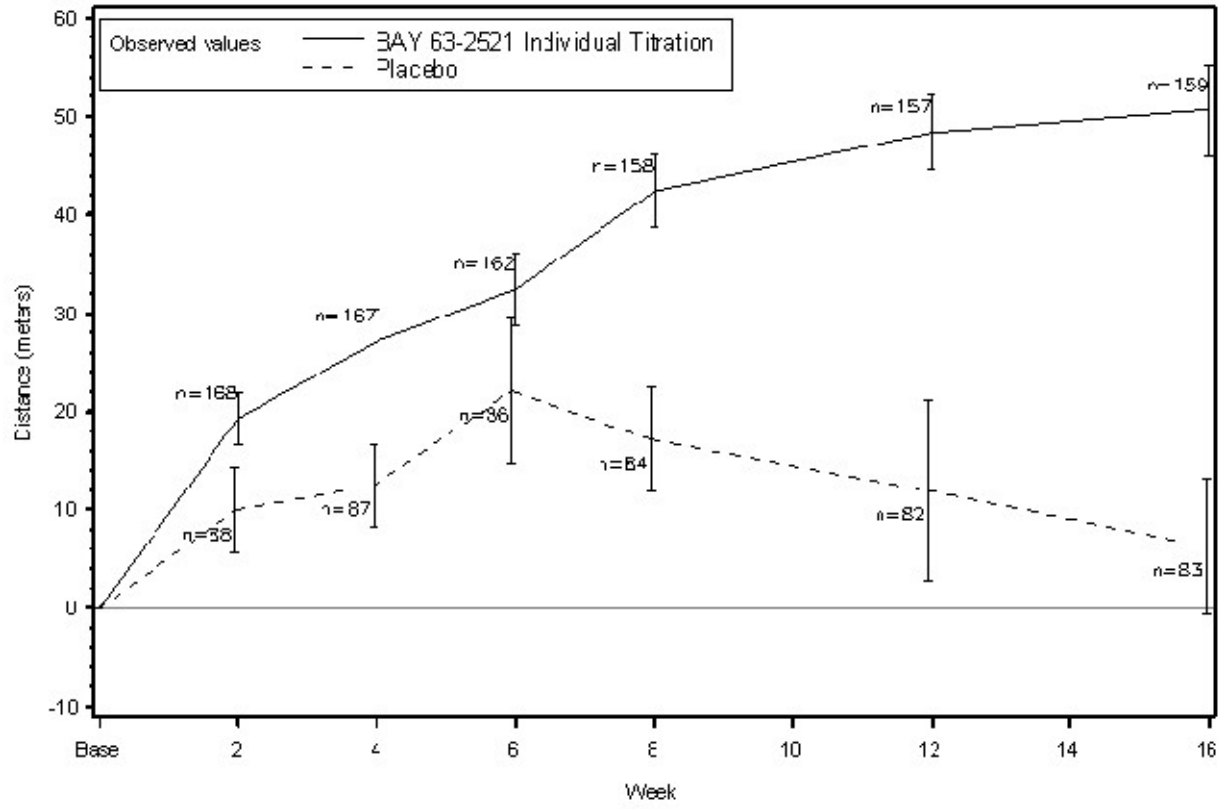
At the end of the 16-week treatment phase, 77% of patients in the riociguat group were on the highest dose of 2.5 mg, 13% were on 2.0 mg and the remainder on lower doses. Eligible patients had the option to enter an open-label extension trial (CHEST-2), where all patients received an individualized optimal dose of riociguat.

Study Results

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 7). 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 8).

Table 7: 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 8: 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 9).

Table 9: 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 8).

A greater improvement in WHO Functional Class was observed in the riociguat IDT group than in the placebo group (see Table 8). 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 8). 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. 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 582.2 days (± 317.4). The probabilities of survival at 1, 2, and 3 years were 97%, 94%, 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.

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 ricoguat group was 63.4 ± 58.7 m (n=115), 64.7 ± 55.3 m (n=98), 62.1 ± 65.7 m (n=63) and

80.3 ± 62.2 m (n=43) at 3-months, 6-months, 12-months and 18-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 43.9 ± 65.8 m (n=57), 40.9 ± 60.8 m (n=51), 17.2 ± 68.9 m (n=30) and 18.6 ± 54.6 m (n=20) at 3-months, 6-months, 12-months and 18-months.

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 3-month, 6-month, 12-month and 18-month into CHEST-2 these improvement/deterioration fractions in the riociguat group were: 43.0%/2.5% (n=121), 52.5%/5.9% (n=101), 57.6%/3.0% (n=66) and 63.6%/4.5% (n=44), 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 3-month, 6-month, 12-month and 18-month into CHEST-2 these improvement/deterioration fractions in the former placebo group were: 38.3%/3.3% (n=60), 37.0%/1.9% (n=54), 33.3%/0% (n=30) and 20.0%/0% (n=20).

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

Study Design and Demographics

This randomized, double-blind, multi-national, multi-centre, placebo controlled, phase III 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).

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 testing performed). Demographics and baseline characteristics were similar between treatment groups.

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) and 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.

Study Results

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

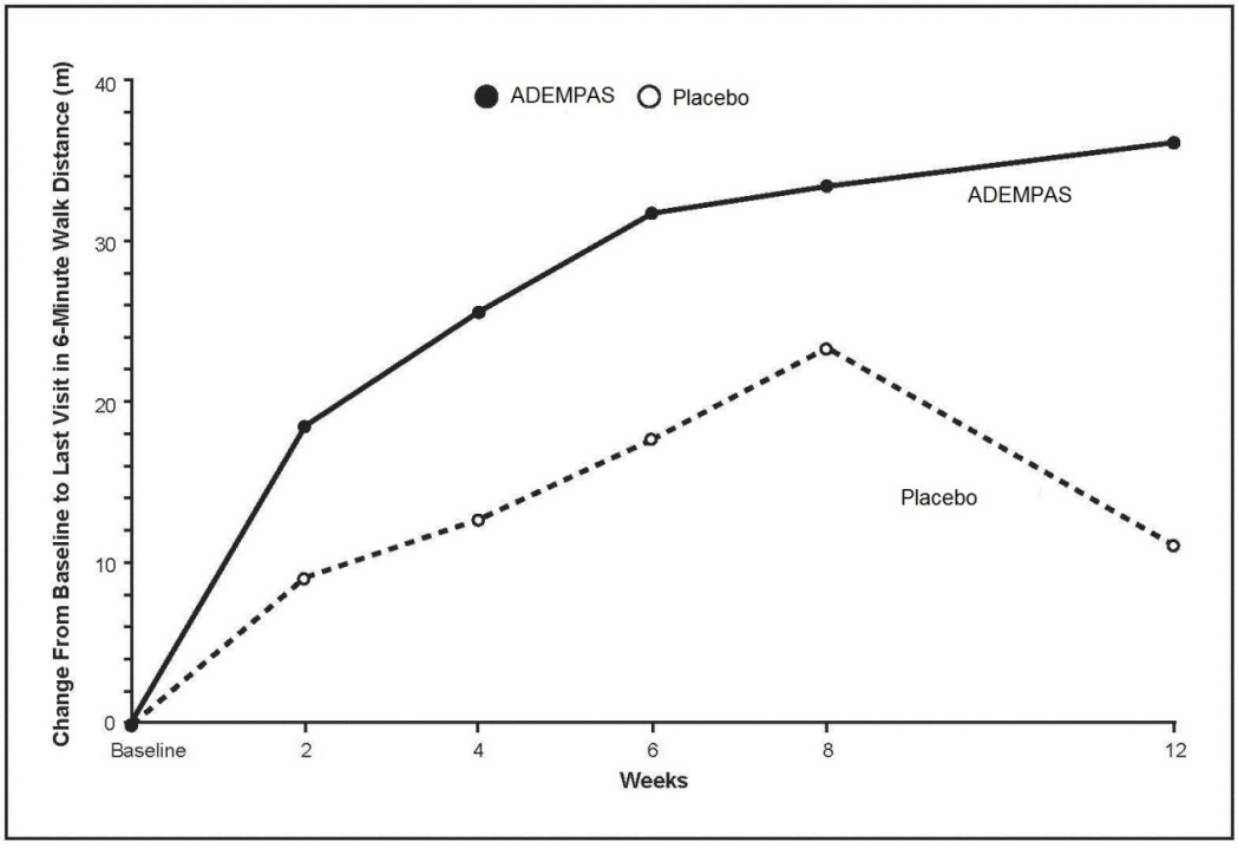
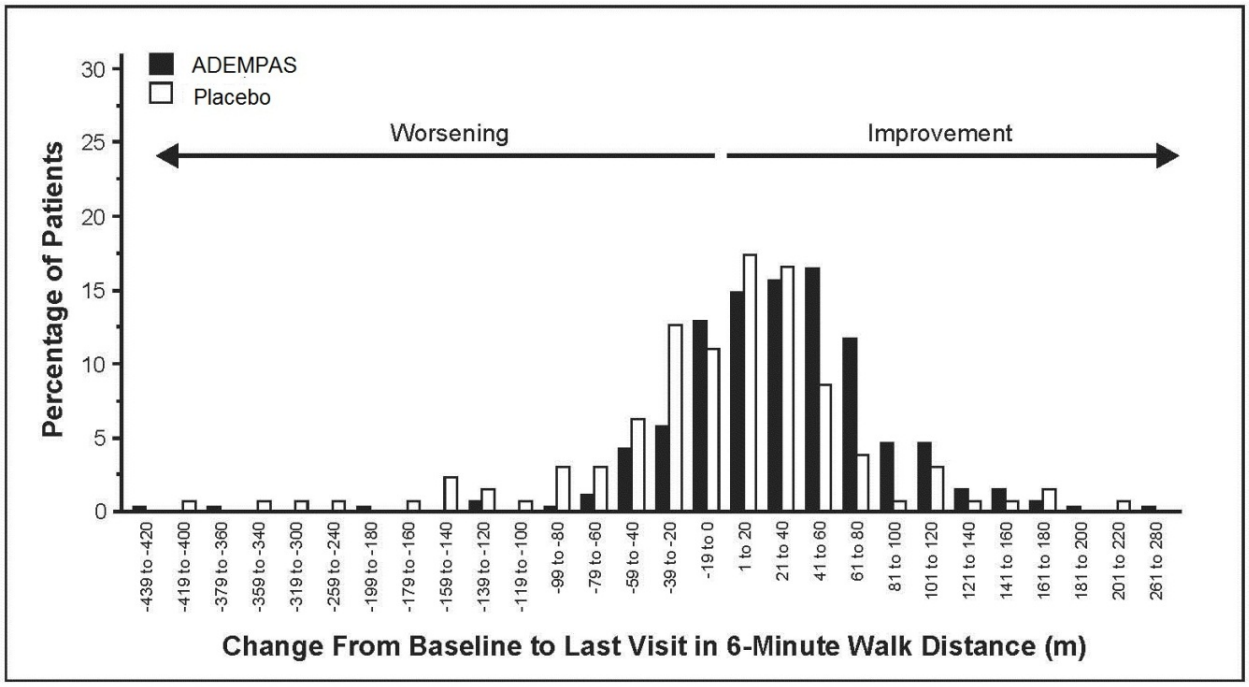


Figure 3 illustrates the results of the ADEMPAS and placebo treatment groups displayed as a histogram summarizing the treatment effect on the 6MWD. The patients are grouped by change in 20 meters from baseline. Overall this figure shows that patients treated with ADEMPAS benefit compared to those treated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

receiving ADEMPAS (76%) experienced an improvement in 6MWD compared to 74 patients (59%) on placebo.

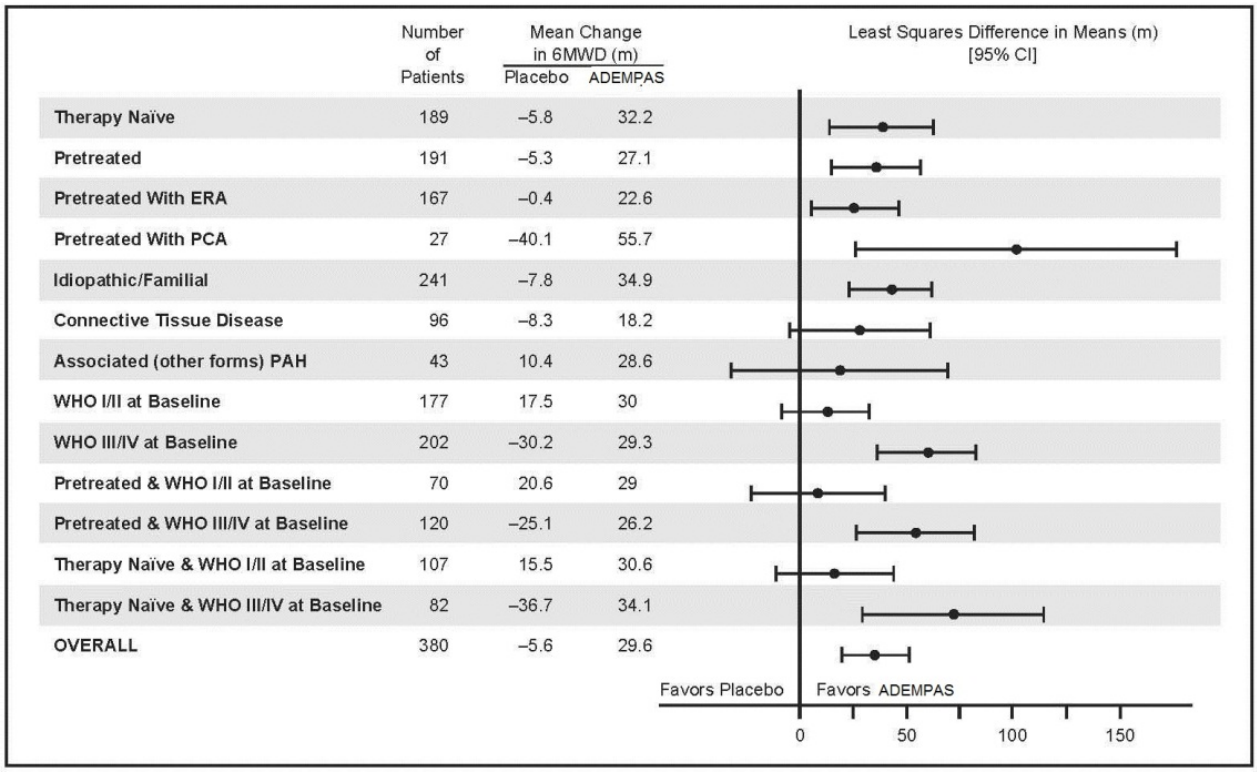
Figure 3: PATENT-1 Distribution of Patients by Change from Baseline in 6-Minute Walk Distance



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 10.

Table 10: 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 11.

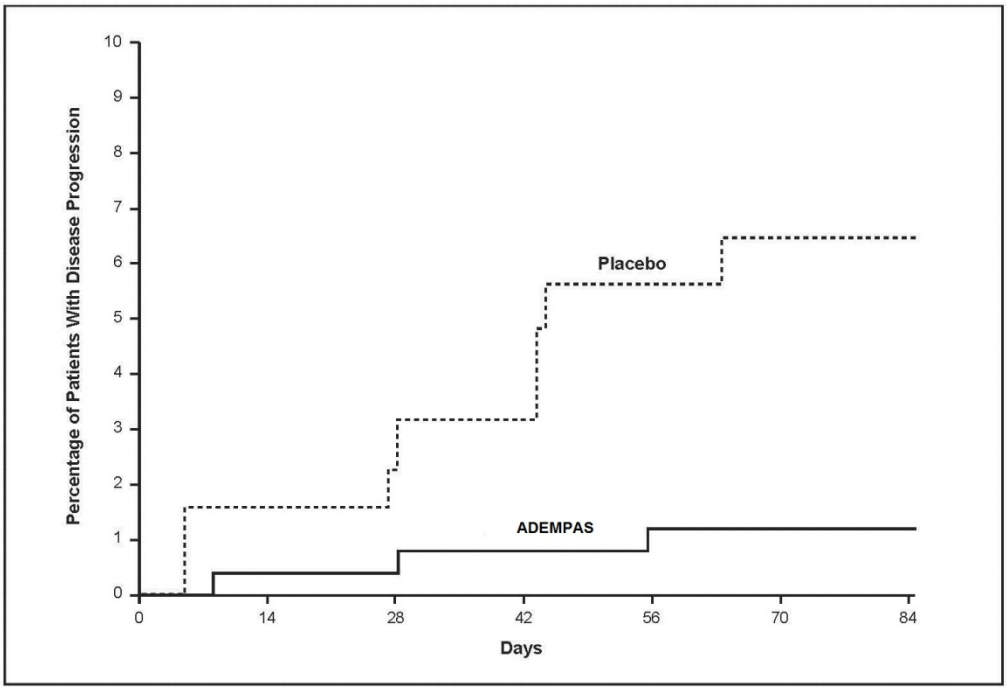
Table 11: Effects of ADEMPAS in PATENT-1 on Events of Clinical Worsening (ITT analysis set)

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 12. Right heart catheterization was performed at the beginning and the end of the study period in 339 patients.

Table 12: 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

Long Term Treatment of PAH

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 663 days (± 319.3). The probabilities of survival at 1, 2, and 3 years were 97%, 93%, and 91%, 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 52.8 m at 6 months (n=366), 52.2 m at 9 months (n=354), 51.4 m at 12 months (n=327) and 49.6m at 18 months (n=245).

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.

DETAILED PHARMACOLOGY

Animal Pharmacology

In all species tested, the toxicological profile of ADEMPAS (riociguat) 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 strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a 'multi-pathway 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}).

Special Populations

Geriatrics

Elderly patients (≥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 DOSAGE AND ADMINISTRATION, Geriatrics (≥65 years of age)).

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 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 WARNINGS AND PRECAUTIONS, Special Populations and 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 DOSAGE AND ADMINISTRATION, 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 WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Hepatic Impairment).

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

Gender, Ethnicity, Weight Categories

Pharmacokinetic studies revealed no relevant differences due to gender, ethnicity or weight in the exposure to riociguat.

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.

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.

Carcinogenicity

In rats, at systemic exposure corresponding up to 7-fold of the human exposure, riociguat was non-carcinogenic.

In the carcinogenicity study in mice, statistically non-significant increases in intestinal tumors were seen at exposure levels slightly less and more than the human therapeutic exposure were considered to be a consequence of chronic nonneoplastic large intestinal lesions including inflammation, mucosal degeneration, and reactive hyperplasia.

Reproductive 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.

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PART III: CONSUMER INFORMATION

PrADEMPAS®

Riociguat Tablets

This leaflet is Part 3 of a three-part "Product Monograph" published when ADEMPAS was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ADEMPAS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ADEMPAS is indicated to treat adult patients with:

- CTEPH (Chronic Thromboembolic Pulmonary Hypertension) (WHO Group 4).

CTEPH is a disease where high blood pressure occurs in lung vessels (pulmonary arteries) which is caused by fixed blood clots hindering the blood flow. High pulmonary blood pressure in the lung vessels means that the heart needs to work harder to pump blood through the lungs. This causes people to feel tired, dizzy and short of breath.

ADEMPAS is intended for use in patients with CTEPH who cannot be operated (inoperable CTEPH) or in patients with persistent or recurrent high pulmonary blood pressure after surgical treatment.

- PAH (Pulmonary Arterial Hypertension) (WHO Group 1)

PAH is a disease where high blood pressure occurs in lung vessels (pulmonary arteries). In patients with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy and short of breath.

What it does:

CTEPH (WHO Group 4):

ADEMPAS contains riociguat, which is a soluble guanylate cyclase (sGC)-stimulator. It works by dilating the pulmonary arteries (the blood vessels that connect the heart to the lungs), lowering the high blood pressure and making it easier for the heart. This leads to an increase in exercise capacity (will increase a patient's ability to walk further) and an improvement of Functional Class (a World Health Organization measure of symptom severity and impact on daily activities).

PAH (WHO Group 1):

ADEMPAS contains riociguat, which is a soluble guanylate cyclase (sGC)-stimulator. It works by dilating the pulmonary arteries (the blood vessels that connect the heart to the lungs), lowering the high blood pressure and making it easier for the heart. This leads to an increase in exercise capacity (will increase a patient's ability to walk further), an improvement of Functional Class (a World Health Organization measure of symptom severity and impact on daily activities) and delayed clinical worsening in patients with PAH.

When it should not be used:

- if you are hypersensitive (allergic) to ADEMPAS or any other ingredients in the tablet.
- if you are pregnant or planning to become pregnant.
- If you are breast-feeding or plan to breast-feed.
- if you are taking **sildenafil (VIAGRA, REVATIO), tadalafil (CIALIS, ADCIRCA), vardenafil (LEVITRA, STAXYN)**, **nitrates** (medicines used to treat high blood pressure or heart disease) or **nitric oxide donors** (such as amyl nitrite) in any form.
- if you have increased pressure in your pulmonary circulation associated with scarring of the lungs, of unknown cause (idiopathic pulmonary pneumonia).

What the medicinal ingredient is:

Riociguat.

What the nonmedicinal ingredients are:

Cellulose microcrystalline, crospovidone, hypromellose 5cP, lactose monohydrate, magnesium stearate, sodium laurilsulfate. The film-coating is composed of ferric oxide red, ferric oxide yellow, hydroxypropylcellulose, hypromellose 3cP, propylene glycol, titanium dioxide.

What dosage forms it comes in:

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

WARNINGS AND PRECAUTIONS

BEFORE you use ADEMPAS talk to your doctor or pharmacist if you have or have had any of the following conditions:

- if you take PDE-5-inhibitors (such as sildenafil or tadalafil) used to **treat high blood pressure in the pulmonary arteries** (pulmonary arterial hypertension) or **male erectile dysfunction** (such as the above or vardenafil).
- if you feel **short of breath** during treatment with ADEMPAS, this can be caused by a build-up of fluid in the lungs (pulmonary veno-occlusive disease). Talk to your doctor.
- if you have recently experienced serious bleeding from the lung, or if you have undergone interventional treatment to stop **coughing up blood** (bronchial arterial embolization). In these cases the risk of bleeding from the lungs may increase further. Inform your doctor if you take medicines used to **prevent blood clots** (anticoagulants). You will be regularly monitored by your doctor.
- if you have **problems with your heart, circulation** or are on antihypertensive therapy.
- if you take medicines used to **treat fungal infections** (e.g. ketoconazole, itraconazole), or medicines for the **treatment of HIV infection** (e.g. ritonavir).
- if you take **medicines against cancer** called tyrosine kinase inhibitors (e.g. erlotinib, gefitinib) or cyclosporine a medicine used to **prevent rejection of transplanted organs**. In this case your doctor will have to check your blood pressure regularly.
- ADEMPAS is not recommended for patients under 18 years of age, because there is no information on its use in children and adolescents.
- Do not take ADEMPAS during pregnancy. If there is a chance you could become pregnant, use reliable forms of contraception while you are taking ADEMPAS. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking ADEMPAS.
- If you are breast-feeding, ask your doctor or pharmacist for advice before taking ADEMPAS because it might harm your baby. A decision must be made whether to discontinue breast feeding or to stop therapy with ADEMPAS.

If you have the following conditions:

- **low blood pressure** (<95 mm Hg) at the beginning of treatment
- **severe liver problems** (hepatic impairment, Child Pugh C)
- **severe kidney problems** (creatinine clearance <15 mL/min or if you are **on dialysis**)

the use of ADEMPAS is not recommended, as there are no studies on the use of ADEMPAS in patients with these conditions.

INTERACTIONS WITH THIS MEDICATION

Drug-drug interaction:

Drugs that may interact with ADEMPAS include:

- **nitric oxide donors** (such as amyl nitrite)
- **nitrates** (medicines used to treat high blood pressure or heart disease)
- PDE-5-inhibitors, [such as sildenafil (VIAGRA, REVATIO) or tadalafil (CIALIS, ADCIRCA)] medicines used to treat high blood pressure in the pulmonary arteries (pulmonary arterial hypertension) or male erectile dysfunction [such as the above or vardenafil (LEVITRA, STAXYN)]
- medicines used to treat fungal infections (e.g. **ketoconazole, itraconazole**)
- medicine for the treatment of HIV infection (e.g. **ritonavir**)
- **cyclosporine** (medicine used to prevent rejection of transplanted organs)
- **erlotinib (TARCEVA)** or **gefitinib (IRESSA)** (medicines against cancer)
- **granisetron** (medicine used to treat nausea and vomiting)
- **phenytoin** and **carbamazepine** (antiepileptic medicines), **phenobarbitone** (antiepileptic medicine, sedative)
- **quinidine** (antiarrhythmic, antimalarial agent)
- **carvedilol** (for the treatment of heart failure and hypertension)

Drug-herb interaction:

- **St. John´s Wort** (herbal treatment for depression)

Drug-food interaction:

- ADEMPAS contains **lactose**. If you have been told by any doctor that you have an intolerance to some sugars, inform your doctor before taking this medicinal product.

Drug-lifestyle interaction:

If you **smoke**, it is recommended that you stop, as smoking may reduce the efficacy of ADEMPAS. Contact your doctor if you stop or start smoking during treatment as a dose adjustment might be required.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

PROPER USE OF THIS MEDICATION

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment should only be initiated and monitored by a doctor experienced in the treatment of CTEPH or PAH.

Usual adult dose:

During the first weeks of treatment your doctor will need to measure your blood pressure at least every two weeks. This is required to decide on the correct dose of your medication (ADEMPAS is available in different strengths (0.5 mg to 2.5 mg)).

Initial treatment dose:

- Starting at one 1 mg tablet, three times daily for 2 weeks. Your physician may have prescribed 0.5 mg 3 times daily for 2 weeks, depending on your health status.
- Tablets should be taken three times a day, approximately 6 to 8 hours apart, with or without food.
- Your doctor will increase the strength of your tablet every 2 weeks to a maximum of 2.5 mg three times a day (maximum daily dose of 7.5 mg) unless you experience any side effects or very low blood pressure. If you may experience any side effects mentioned *(see below section 'SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM')*, contact your doctor.

Maintenance dose:

Your doctor will continue to prescribe you ADEMPAS at the highest dose you are comfortable on unless you experience any side effect or very low blood pressure, symptoms like dizziness and fainting.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

You may experience the side effects mentioned below (*see section 'SIDE EFFECTS WHAT TO DO ABOUT THEM'*).

Contact your doctor, he or she will treat any symptoms that follow.

Missed dose:

Do not take a double dose to make up for a forgotten dose. If a dose is missed, treatment should be continued with the next dose as planned.

Stopped treatment:

Don't stop taking ADEMPAS without talking to your doctor first, because this medicine prevents the development of a serious condition.

In case treatment has to be interrupted for 3 days or more, please contact your doctor before restart of treatment.

Special considerations for patients with liver or kidney problems:

You should tell your doctor if you have liver or kidney problems. Your dose may need to be adjusted.

If you have severe liver problems (hepatic impairment, Child Pugh C) or severe kidney problems (creatinine clearance <15 mL/min or if you are on dialysis) you should not take ADEMPAS, as there are no data on the use of ADEMPAS in patients with these conditions.

65 years or older:

If you are 65 years or older your doctor will take extra care in adjusting your dose of ADEMPAS.

Other medicines:

Medicines used to treat stomach disease or heartburn, such as aluminum hydroxide/magnesium carbonate should be taken at least 1 hour after ADEMPAS.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most **serious** side effects are **coughing up blood** (hemoptysis) and **bleeding from the lungs** (pulmonary hemorrhage); cases with fatal outcome were observed.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Very common	Headache, dizziness	✓		
	Indigestion	✓		
	Swelling of limbs (edema peripheral)	✓		
	Nausea		✓	
	Diarrhea		✓	
	Vomiting		✓	
Common	Pain in stomach and bowels (gastrointestinal or abdominal pain), bloating, constipation or heartburn (gastroesophageal reflux disease)	✓		
	Reduction in red blood cells which can make your skin pale and cause weakness, tiredness, dizziness, headache, breathlessness, unusually fast heartbeat, or chest pain		✓	
	Unusually fast or irregular heartbeats (palpitations)		✓	
	Low blood pressure (lightheaded-ness, dizziness)		✓	
	Coughing up blood (mild to moderate)		✓	
	Nosebleed lasting more than 5 minutes		✓	
	Congestion in the nose (nasal congestion)		✓	
	Difficulty in swallowing		✓	
Uncommon	Bleeding from the lung/coughing up blood (severe)			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown	Allergic reactions (symptoms like sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.)			✓

This is not a complete list of side effects. For any unexpected effects while taking ADEMPAS, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach and sight of children. Store at room temperature between 15°C and 30°C. Do not use after the expiry date stated on the label.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at
1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number and email address.

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Bayer