PRODUCT INFORMATION

ADEMPAS® (riociguat)

ADEMPAS may cause birth defects and is contraindicated in pregnancy.

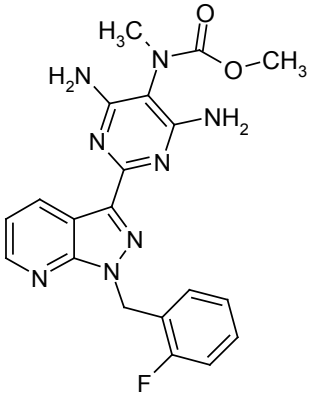
(see CONTRAINDICATIONS and PRECAUTIONS)

NAME OF THE MEDICINE

Adempas (riociguat) 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets for oral administration.

The chemical formula for riociguat is methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate.

Riociguat has the following structural formula:



$C_{20}H_{19}FN_8O_2$

CAS number: 625115-55-1

DESCRIPTION

Riociguat is a white to yellowish, crystalline, non-hygroscopic substance with a relative molecular mass of 422.42 g/mol. 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 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.

Each round film-coated tablet contains 0.5 mg, 1 mg, 1.5 mg, 2 mg or 2.5 mg riociguat and the inactive ingredients are cellulose microcrystalline, crospovidone, hypromellose, lactose, magnesium stearate, sodium lauryl sulfate. The film coating contains the following inactive ingredients hydroxypropylcellulose, hypromellose, propylene glycol, titanium dioxide. Adempas 1 mg, 1.5 mg, 2 mg and 2.5 mg tablets contain in addition iron oxide yellow and Adempas 2 mg and 2.5 mg tablets contain in addition iron oxide red.

PHARMACOLOGY

Pharmacodynamic Properties

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme found in most tissues and the receptor for nitric oxide (NO).

When NO binds to sGC, the enzyme catalyses synthesis of the signalling 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 (PH) 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 sensitises sGC to endogenous NO by stabilising 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.

Pharmacokinetic Properties

Absorption

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

Intake with food does not affect riociguat area under the concentration curve (AUC) or C_{max} to a clinically relevant extent. 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, catalysed by CYP1A1, CYP3A4, CYP2C8 and CYP2J2, is the major biotransformation pathway of riociguat leading to its major circulating active metabolite (pharmacological activity: 1/10 to 1/3 of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.

CYP1A1 catalyses the formation of riociguat's main metabolite in liver, lungs and intestines 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 – 45%) and biliary/faecal routes (48 – 59%). Approximately 4 to 19% of the administered dose is

excreted as unchanged riociguat via the kidneys. Approximately 9 – 44% of the administered dose is excreted as unchanged riociguat in faeces.

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 – 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

Riociguat pharmacokinetics are linear from 0.5 to 2.5 mg.

Inter-individual variability (CV%) of riociguat exposure (AUC) across all doses is approximately 60%.

Geriatric Patients

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, Special Populations).

Patients with Hepatic Impairment

In cirrhotic patients (non-smokers) with mild hepatic impairment (classified as Child Pugh A) riociguat mean AUC was increased by 35% compared to healthy controls, which is within normal intra-individual variability. In cirrhotic patients (non-smokers) with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 51% compared to healthy controls. (see DOSAGE AND ADMINISTRATION, Special Populations).

There are no data in patients with pulmonary hypertension with severe hepatic impairment (classified as Child Pugh C), patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied. Therefore use of Adempas is not recommended in these patients (see DOSAGE AND ADMINISTRATION, Special Populations and PRECAUTIONS, Hepatic Impairment).

Patients with Renal Impairment

Overall, mean dose- and weight- normalised 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 non-smoking individuals with mild (Stage 2 Chronic Kidney Disease (CKD), creatinine clearance 50 – 80 mL/min), moderate (Stage 3 CKD, creatinine clearance 30 – 49 mL/min) or severe (Stage 4 CKD, creatinine clearance 15 – 29 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively (see DOSAGE AND ADMINISTRATION, Special Populations).

There are no data in patients with pulmonary hypertension with creatinine clearance < 15 mL/min or on dialysis (Stage 5 CKD). Therefore use is not recommended in patients with creatinine clearance < 15 mL/min or on dialysis (see DOSAGE AND ADMINISTRATION, Special Populations and PRECAUTIONS, Renal Impairment).

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

Gender, Inter-Ethnic Differences, Weight Categories

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

Pharmacokinetic / Pharmacodynamic Relationships

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

CLINICAL TRIALS

Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

A randomised, double-blind, multi-national, multi-centre, placebo-controlled Phase III study (CHEST-1) was conducted in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Patients were included if they:

- were technically inoperable for pulmonary endarterectomy, with pulmonary vascular resistance (PVR) >300 dyn*sec*cm-5 and mean pulmonary artery pressure >25 mmHg measured at least 90 days after the start of full anticoagulation, or

- had recurrent or persisting pulmonary hypertension defined as PVR > 300 dyn*sec*cm-5 measured at least 180 days following pulmonary endarterectomy.

The patient population included male and female patients between the age of 18 and 80, of which 72% of patients had inoperable CTEPH and 28% had recurrent or persisting CTEPH following pulmonary endarterectomy.

Patients had a World Health Organization (WHO) Functional Class I (1%) or II (31%) or III (64%) or IV (4%) at baseline. The mean baseline six minute walking distance (6MWD) was 347 m. All patients were treatment naïve (patients on PAH specific medication were excluded). Patients with systolic blood pressure < 95 mmHg were excluded from the study. Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers and oxygen were allowed, but not concomitant therapy with NO donors, endothelin receptor antagonists, prostacyclin analogues, specific PDE-5 inhibitors (such as, sildenafil, tadalafil, or vardenafil), and nonspecific phosphodiesterase inhibitors (for example, dipyridamole or theophylline).

CHEST-1 included 261 patients treated and valid for safety analysis randomised to one of two treatment groups: Adempas individual dose titration (IDT) up to 2.5 mg TDS (n=173, referred to as riociguat group), or placebo (n=88). During an 8 week titration phase, the dose of Adempas was titrated every 2 weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension. An individualised dose was reached at the end of the titration. 77% of patients were titrated to the maximum dose of 2.5 mg TDS and 13%, 6%, 4%, and 1% of patients received Adempas 2 mg, 1.5 mg, 1 mg, and 0.5 mg TDS, respectively.

Statistical Analysis of Efficacy Endpoints

All p-values are based on stratified Wilcoxon test (unless a different test is mentioned). All 95% Confidence Interval (CI) and treatment effects are based on analysis of covariance (ANCOVA).

Primary Endpoint

The primary endpoint was the change from baseline at week 16 (last visit) in 6MWD compared to placebo. Results of the 6MWD at 16 weeks are shown in Table 1 and Figure 1.

Improvements in walking distance were apparent from week 2 onward, and at week 16 (n=261) the mean increase in 6MWD within the riociguat group was 46 m (95% CI: 25 m to 67 m; p<0.0001) compared to placebo (ITT analysis, see Table 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 (95% CI: 29 m to 79 m), and patients with recurrent or persisting CTEPH following pulmonary endarterectomy (n=72) demonstrated an increase in 6MWD of 27 m (95% CI: -10 m to 63 m).

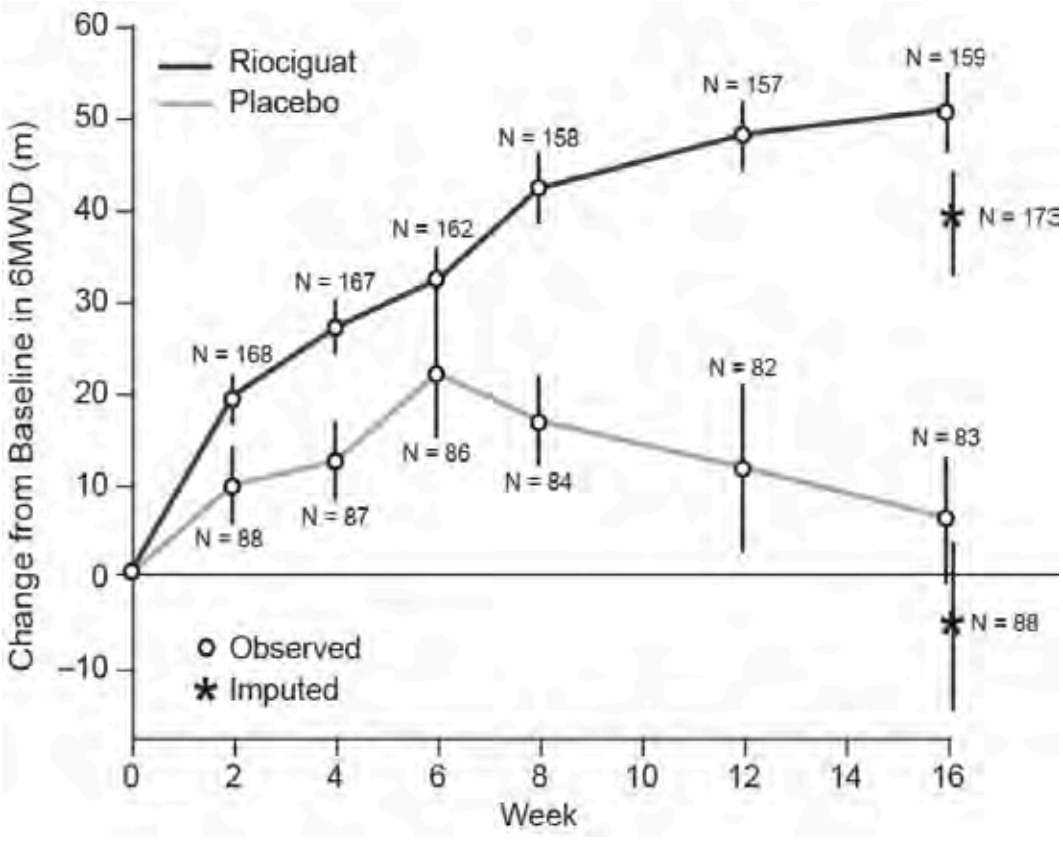
Table 1. Effects of riociguat on 6MWD in CHEST 1 at week 16 (last visit; ITT analysis set)

Entire patient population	**Riociguat (IDT) n=173**	**Placebo n=88**
Baseline (m) [SD]	342 [82]	356 [75]
Change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-corrected difference (m) 95% CI ; (p-value)	46 25 m to 67 m; (<0.0001)	
Inoperable patient population	**Riociguat (IDT) n=121**	**Placebo n=68**
Baseline (m) [SD]	335 [83]	351 [75]
Change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-corrected difference (m) 95% CI	54 29 m to 79 m	
Patient population with CTEPH post- pulmonary endarterectomy	**Riociguat (IDT) n=52**	**Placebo n=20**
Baseline (m) [SD]	360 [78]	374 [72]
Change from baseline (m) [SD]	27 [68]	2 [73]
Placebo-corrected difference (m) 95% CI	27 -10 m to 63 m	
WHO Functional Class I/II at baseline	**Riociguat (IDT) n=52**	**Placebo n=25**
Baseline (m) [SD]	387 [59]	386 [64]
Change from baseline (m) [SD]	46 [80]	20 [51]
Placebo-corrected difference (m) 95% CI	25 -9 m to 60 m	
WHO Functional Class III/IV at baseline	**Riociguat (IDT) n=115**	**Placebo n=62**
Baseline (m) [SD]	320 [83]	342 [74]
Change from baseline (m) [SD]	36 [79]	-16 [94]

Placebo-corrected difference (m) 95% CI	53 27 m to 79 m	
All male subjects	**Riociguat (IDT) n=55**	**Placebo n=34**
Baseline (m) [SD]	359 [75]	377 [69]
Change from baseline (m) [SD]	54 [81]	22 [71]
Placebo-corrected difference (m) 95% CI	40 9 m to 71 m	
All female subjects	**Riociguat (IDT) n=115**	**Placebo n=62**
Baseline (m) [SD]	335 [84]	343 [76]
Change from baseline (m) [SD]	32 [78]	-23 [88]
Placebo-corrected difference (m) 95% CI	54 28 m to 81 m	

IDT: Individual dose titration

Figure 1: 6-Minute Walk Distance Over 16 Weeks



Last visit = last observed value—not including follow-up—for patients who completed the study or withdrew, except imputed worst value (zero) in case of death or clinical worsening without a termination visit or a measurement at that termination visit.

Secondary Endpoints

Improvements in walking distance were complemented with consistent improvements in clinically relevant secondary endpoints.

A statistically significant improvement for the riociguat group over placebo was shown for the following secondary efficacy variables:

- Pulmonary vascular resistance (PVR): Significantly reduced PVR (placebo-corrected mean change from baseline of -246 dyn*s*cm^{-5}; 95% CI -303 to -190; p<0.0001; see Table 3).

- NT-proBNP: Significantly reduced NT-proBNP (placebo-corrected mean change from baseline -444 ng/L, 95% CI -843 to -45, p<0.0001).

- WHO functional class: Significant improvement of at least one functional class in the riociguat group at week 16 (last visit) of 33% vs. 15% in the placebo group and a deterioration of at least one functional class was observed in 5% of patients in the riociguat group vs. 7% in the placebo group (p=0.0026; see Table 2). Functional class was unchanged in 62% of patients in the riociguat group vs. 78% in the placebo group.

Table 2. Effects of riociguat on the change in Functional Class in CHEST-1 at week 16 (last visit; ITT analysis set)

Change in 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		

No statistically significant (below threshold of hierarchical testing[1]) result was found for:

Time to clinical worsening, Borg CR 10 scale, European quality of life (EQ-5D) and Living with Pulmonary Hypertension (LPH) questionnaire.

A trend towards lower incidence of clinical worsening events by week 16 (last visit) in patients treated with riociguat (2.3%) compared to placebo (5.7%) was observed (p=0.1724, Stratified log-rank test).

Haemodynamic Parameters

Right heart catheterisation was performed at the beginning and the end of the placebo-controlled study period in 233/261 (89%) patients to generate a comprehensive set of cardiopulmonary haemodynamic data (see Table 3).

A statistically significant reduction of PVR (see above) was shown in the riociguat group vs. placebo. The improvement seen for PVR was also observed in other relevant haemodynamic

[1] All subsequent endpoints cannot be considered statistically significant in a formal sense because statistical significance was not achieved for Time to clinical worsening in the hierarchical testing of the secondary efficacy variables.

parameters including mean pulmonary artery pressure (PAP_{mean}) (-5.0 mmHg) and an increase in cardiac index (0.47 L/min/m^2).

Table 3. CHEST-1, change in haemodynamic parameters from baseline to last visit: Comparison of riociguat 1.0 – 2.5 mg (RIO) and placebo (PBO) (ITT analysis set)

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

* PVR was a secondary endpoint in the study
All other parameters were not pre-specified as endpoints

Long-term Treatment of CTEPH

An open label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In the interim analysis, the mean treatment duration at the cut-off date was 388 days with a median duration of 336 days (range 15 to 989 days) and a total riociguat exposure of 206 patient years.

The long-term 6MWD data from CHEST-2 (open label) indicate maintenance of the riociguat treatment effect that was observed in the main (controlled) phase of the study. The probability of survival at 1-year was 98%.

Treatment of Pulmonary Arterial Hypertension (PAH)

A randomised, double-blind, multi-national, multi-centre, placebo-controlled, Phase III study (PATENT-1) was conducted in patients with pulmonary arterial hypertension (PAH) who were either treatment-naïve or pre-treated with an endothelin receptor antagonist (ERA) or a prostacyclin analogue (inhaled, oral or subcutaneous).

The overall patient population included male (21%) and female (79%) patients who were between the age of 18 and 80 years (mean age = 50.6 years) and had been diagnosed with either idiopathic PAH (61%), familial PAH (2%), PAH associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or associated PAH due to anorexigen or amphetamine (1%) use.

Unspecific treatments which may also be used for the treatment of PH such as oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation were permitted in the study. Patients with systolic blood pressure of < 95 mmHg at initiation were excluded.

In addition, patients with cardiovascular diseases including clinically significant cardiovascular disease, uncontrolled hypertension, atrial flutter, atrial fibrillation, left heart failure, symptomatic atherosclerotic disease and severe coronary artery disease were excluded.

Patients had a WHO Functional Class I (3%) or II (42%) or III (54%), or IV (1%) at baseline, with 50% of patients treatment naïve, 44% pre-treated with ERAs and 7% with prostacyclin analogues (of which, 32% by oral, 45% by inhalation and 23% by subcutaneous administration, intravenous prostanoids were not studied). The overall mean baseline 6MWD was 363 m.

PATENT-1 included 443 patients treated and valid for safety analysis, randomised to one of three treatment groups: Adempas individual dose titration up to 2.5 mg TDS (n=254); placebo (n=126); and a "capped" Adempas dose titration up to 1.5 mg TDS (n=63; exploratory dose arm, no statistical testing performed). Adempas was added in combination in patients pre-treated with an ERA or a prostacyclin analogue.

Patients were initiated on treatment at 1 mg TDS. During an 8-week titration phase, the dose of Adempas was titrated every 2 weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension. An individualised dose was reached at the end of the titration. Approximately 75% of patients were up-titrated to receive the maximum dose of 2.5 mg TDS by week 12 and 15%, 6%, 3%, and 2% received 2 mg, 1.5 mg, 1 mg, and 0.5 mg respectively.

Statistical Analysis of Efficacy Endpoints

The pre-specified primary analysis is with the Adempas 2.5 mg treatment arm (referred to as riociguat group) compared to placebo. All p-values are based on stratified Wilcoxon test (unless a different test is mentioned). All 95% CI and treatment effects are based on analysis of covariance (ANCOVA).

Primary Endpoint

The primary endpoint was the change from baseline at week 12 (last visit) in 6MWD compared to placebo. Results of the 6MWD at 12 weeks are shown in Table 4 and Figure 2.

Improvements in walking distance were apparent from week 2 onward, and at week 12 for the riociguat group was 36 m (95% CI: 20 m to 52 m; $p<0.0001$) compared to placebo (ITT analysis, see Table 4). Improvements of riociguat over placebo were observed in all sub-groups evaluated. Treatment-naïve patients (n=189) demonstrated an increased 6MWD of 38 m (95% CI: 14 m to 62 m).

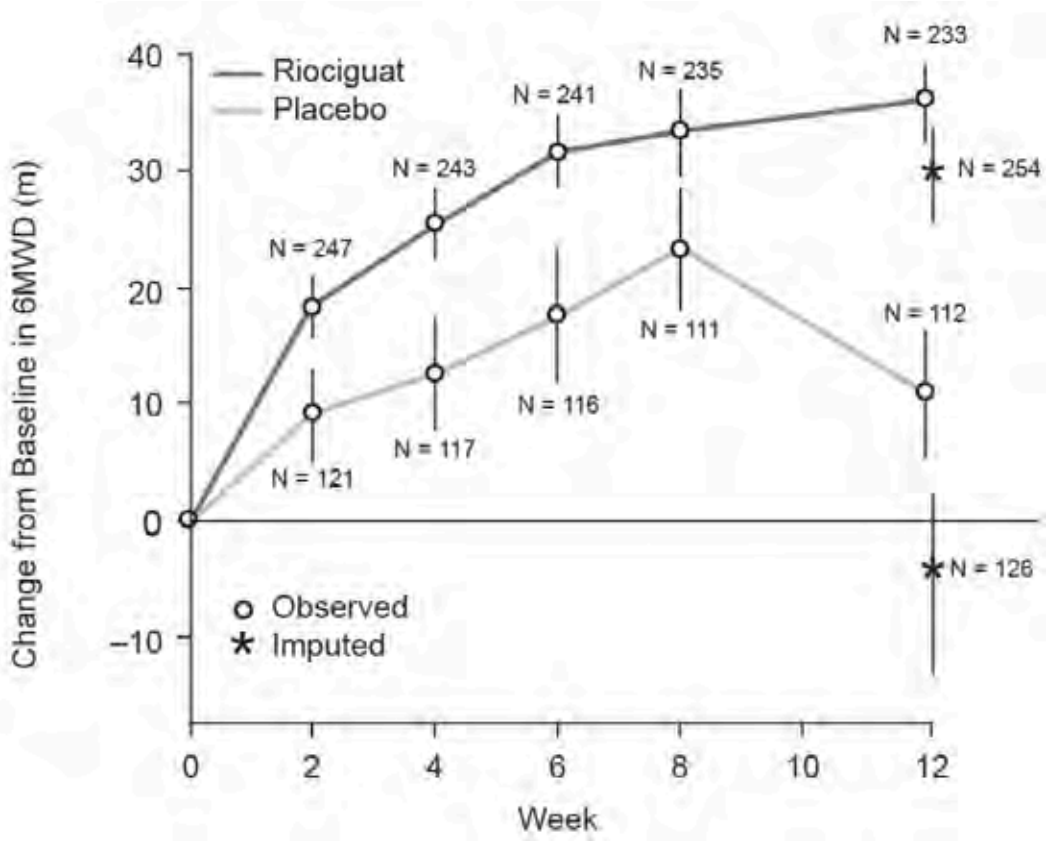
Pre-treated patients (n=191) demonstrated an increased 6MWD of 36 m (95% CI: 15 m to 56 m). Further subgroup analysis of patients pre-treated with ERAs (n=167) revealed a treatment effect estimate of 26 m, (95% CI: 5 m to 46 m). In patients pre-treated with prostacyclin analogues[2] (n=27), the estimated treatment effect was 101 m, (95% CI: 27 m to 176 m).

[2] Three patients were pre-treated with an ERA and prostacyclin analogue at the same time.

Table 4. Effects of riociguat on 6MWD in PATENT-1 at week 12 (last visit; ITT analysis set)

Entire patient population	**Riociguat (IDT) n=254**	**Placebo n=126**
Baseline (m) [SD]	361 [68]	368 [75]
Change from baseline (m) [SD]	30 [66]	-6 [86]
Placebo-corrected difference (m) 95% CI, (p-value]	36 20 m to 52 m, (<0.0001)	
Treatment-naïve patient population	**Riociguat (IDT) n=123**	**Placebo n=66**
Baseline (m) [SD]	370 [66]	360 [80]
Change from baseline (m) [SD]	32 [74]	-6 [88]
Placebo-corrected difference (m) 95% CI	38 14 m to 62 m	
Pre-treated patient population	**Riociguat (IDT) n=131**	**Placebo n=60**
Baseline (m) [SD]	353 [69]	376 [68]
Change from baseline (m) [SD]	27 [58]	-5 [83]
Placebo-corrected difference (m) 95% CI	36 15 m to 56 m	
Idiopathic / Familial	**Riociguat (IDT) n=156**	**Placebo n=85**
Baseline (m) [SD]	365 [67]	369 [74]
Change from baseline (m) [SD]	35 [67]	-8 [83]
Placebo-corrected difference (m) 95% CI	43 23 m to 62 m	
Connective tissue disease	**Riociguat (IDT) n=71**	**Placebo n=25**
Baseline (m) [SD]	348 [70]	361 [88]
Change from baseline (m) [SD]	18 [51]	-8 [110]
Placebo-corrected difference (m) 95% CI	28 -4 m to 61 m	
Other forms of PAH	**Riociguat (IDT) n=27**	**Placebo n=16**
Baseline (m) [SD]	375 [67]	371 [56]
Change from baseline (m) [SD]	29 [91]	10 [52]
Placebo-corrected difference (m) 95% CI	18 -33 m to 69 m	
WHO Functional Class I/II at baseline	**Riociguat (IDT) n=113**	**Placebo n=64**
Baseline (m) [SD]	391 [51]	394 [59]
Change from baseline (m) [SD]	30 [67]	18 [63]
Placebo-corrected difference (m) 95% CI	12 -8 m to 32 m	
WHO Functional Class III/IV at baseline	**Riociguat (IDT) n=141**	**Placebo n=61**
Baseline (m) [SD]	338 [70]	341 [80]
Change from baseline (m) [SD]	39 [65]	-30 [99]
Placebo-corrected difference (m) 95% CI	60 36 m to 83 m	

Figure 2: 6-minute Walk Distance Over 12 Weeks



Last visit = last observed value—not including follow-up—for patients who completed the study or withdrew, except imputed worst value (zero) in case of death or clinical worsening without a termination visit or a measurement at that termination visit.

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.

A *post hoc* analysis was conducted in patients with PAH associated with congenital heart disease who underwent surgical correction for their atrial septal defect or ventricle septal defect. A placebo-corrected treatment response of 41 m (95% CI -0.5 to 82.6) in the 6MWD was observed.

Secondary Endpoints

Improvements in walking distance were complemented with consistent improvements in clinically relevant secondary endpoints.

A statistically significant improvement for the riociguat group over placebo was shown for the following secondary efficacy variables:

- Pulmonary vascular resistance (PVR): Significantly reduced PVR (placebo-corrected mean change from baseline of -226 dyn*s*cm^{-5}; 95% CI -281 to -170; p<0.0001; see Table 7).
- NT-proBNP: Significantly reduced NT-proBNP (placebo-corrected mean change from baseline -432 ng/L, 95% CI -782 to -82; p<0.0001; see Table 7).

- WHO functional class: Significant improvement of at least one functional class in the riociguat group at week 12 (last visit) of 21% vs. 14% in the placebo group and a deterioration of at least one functional class was observed in 4% of patients in the riociguat group vs. 14% in the placebo group (p = 0.0033; see Table 5 and Table 7). Functional class was unchanged in 76% of patients in the riociguat group vs. 71% in the placebo group.

- Time to clinical worsening: Riociguat-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 riociguat (1.2%) compared to placebo (6.3%) (see Table 6 and Table 7).

- Borg CR 10 scale: Significant improvement in Borg CR 10 scale (-0.4 for riociguat vs. +0.1 for placebo, p=0.0022; see Table 7).

No statistically significant (below threshold of hierarchical testing[3]) result was found for the European quality of life (EQ-5D) and Living with Pulmonary Hypertension (LPH) questionnaires (see Table 7).

Table 5. Effects of riociguat on the change in Functional Class in PATENT-1 at week 12 (last visit; ITT analysis set)

Change in Functional Class	Riociguat (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		

Table 6. Effects of riociguat in PATENT-1 on events of clinical worsening (ITT analysis set)

Clinical Worsening Events	Riociguat (IDT) (n=254)	Placebo (n=126)
Patients with any clinical worsening*	3 (1.2%)	8 (6.3%)
Death	2 (0.8%)	3 (2.4%)
Hospitalisations 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 PH	0	1 (0.8%)
Start of new PH treatment	1 (0.4%)	5 (4.0%)

Note: Patients may have had more than one event of clinical worsening

Table 7. Summary of efficacy results for pre-defined variables in the hierarchical testing order – PATENT-1, ITT analysis set

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value
6MWD (m) (primary)	36	20 to 52	<0.0001
PVR (dyn*s* cm^{-5})	-226	-281 to -170	<0.0001
NT-proBNP (pg/mL)	-432	-782 to -82	<0.0001
WHO Functional Class	20.9%[a] riociguat 14.4% [a] placebo	N/A	0.0033
Time to clinical worsening	1% [b] riociguat 6% [b] placebo	N/A	0.0046[c]

[3] All subsequent endpoints cannot be considered statistically significant in a formal sense because statistical significance was not achieved for EQ-5D in the hierarchical testing of the secondary efficacy variables.

Borg CR 10 scale [d]	-0.4 [e] riociguat 0.1 [e] placebo	N/A	0.0022

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

a Improvement by at least 1 WHO Functional Class in the respective treatment group
b Percentage of subjects with any clinical worsening event in the respective treatment group
c Stratified log-rank test p-value for time to clinical worsening.
d Subjects enrolled before amendment 4 used the Modified Borg Dyspnoea Scale.
e Change from baseline to last visit in the respective treatment group

Haemodynamic Parameters:

Right heart catheterisation was performed at the beginning and at the end of the placebo-controlled study period in 339/380 (89%) patients to generate a comprehensive set of cardiopulmonary haemodynamic data (see Table 8).

A statistically significant reduction of PVR (see above) was shown in the riociguat group vs. placebo. The improvement seen for PVR was also observed in other relevant haemodynamic parameters including mean pulmonary artery pressure (PAP_{mean}) (-3.83 mmHg) and an increase in cardiac index (0.56 L/min/m^2).

Table 8. PATENT-1, change in haemodynamic parameters from baseline to last visit: Comparison of riociguat 1.0 – 2.5 mg (RIO) and placebo (PBO) - ITT analysis set

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

* PVR was a secondary endpoint in the study
All other parameters were not pre-specified as endpoints

Long-term Treatment of PAH

An open label extension study (PATENT-2) included 363 patients who had completed PATENT-1. The mean treatment duration in PATENT-2 at the cut-off date was 438 days with a median duration of 441 days (range 1 to 1078 days) and a total riociguat exposure of 436 patient years.

The long-term 6MWD data from PATENT-2 (open label) indicate maintenance of the riociguat treatment effect that was observed in the main (controlled) phase of the study.

However, without a control group, these data must be interpreted cautiously. The probability of survival at 1-year was 96%.

INDICATIONS

Pulmonary arterial hypertension

Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension
- heritable pulmonary arterial hypertension
- pulmonary arterial hypertension associated with connective tissue diseases or
- pulmonary arterial hypertension associated with congenital heart disease

in adult patients with WHO functional Class II, lll or IV symptoms

Chronic thromboembolic pulmonary hypertension

Adempas is indicated for the treatment of:

- Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or
- inoperable CTEPH

in adult patients with WHO functional Class II, lll or IV symptoms

CONTRAINDICATIONS

Adempas is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Adempas is contraindicated during pregnancy and lactation (see boxed warning, PRECAUTIONS, Use in Pregnancy, Use in Lactation).

Women of child-bearing potential who may become pregnant and not using reliable contraception (see Use in Pregnancy). Women must not become pregnant for at least 1 month after stopping treatment with Adempas.

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see INTERACTIONS WITH OTHER MEDICINES, Pharmacodynamic Interactions).

Co-administration of Adempas with specific PDE-5-inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated (see INTERACTIONS WITH OTHER MEDICINES, Pharmacodynamic Interactions).

PRECAUTIONS

Additional Information on Special Populations

Studies with riociguat have been mainly performed in PAH and CTEPH patients classified as WHO functional Class II and III. Riociguat has only been studied in a limited number of patients with WHO functional Class IV.

The efficacy and safety of riociguat when co-administered with epoprostenol has not been established.

In cigarette smokers riociguat exposure is reduced by 50 – 60%. Therefore patients are advised to stop smoking (see DOSAGE AND ADMINISTRATION, Special Populations).

Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischaemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong multi-pathway CYP and P-gp/BCRP inhibitors.

While the risk of hypotension is greater during titration it may occur during maintenance therapy. Dose reduction should be considered if the patient develops signs or symptoms of hypotension.

Patients with systolic blood pressure < 95 mmHg at treatment initiation have not been studied and therefore the use of Adempas is not recommended. See CLINICAL TRIALS for information of patients excluded from the trials where caution is advised.

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 these patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with Adempas should be discontinued.

Bleeding

In patients with pulmonary hypertension, there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy.

Bleeding risk should be carefully evaluated before initiating Adempas therapy, and patients should be monitored periodically, particularly in patients taking anticoagulants. The prescriber should regularly assess the benefit-risk with each individual patient.

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 haemoptysis including those managed by bronchial arterial embolization. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolization.

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% (12/490) of patients taking Adempas compared to 0% (0/214) of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking Adempas compared to 0% (0/214) placebo patients, including one event with fatal outcome. Serious haemorrhagic events also included 2 patients with vaginal haemorrhage, 2 with catheter site haemorrhage, and 1 each with subdural haematoma, haematemesis, and intra-abdominal haemorrhage.

Concomitant Use with Other Medicinal Products

The concomitant use of Adempas with strong multi-pathway CYP and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to a pronounced increase in riociguat exposure (see INTERACTIONS WITH OTHER MEDICINES, Pharmacokinetic Interactions).

The concomitant use of Adempas with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/BCRP inhibitors, such as the immunosuppressive agent cyclosporin, may increase riociguat exposure (see INTERACTIONS WITH OTHER MEDICINES, Pharmacokinetic Interactions).

These medicines may increase riociguat exposure which may cause hypotension. Therefore, they should be used with caution. Blood pressure should be monitored and dose reduction of riociguat considered.

Food and Dairy Products

No clinically relevant interaction with food was observed (see PHARMACOLOGY, Pharmacokinetic Properties).

Renal Impairment

Patients with mild, moderate or severe renal impairment (Stage 2 – 4 CKD, creatinine clearance 80-15 mL/min) showed a higher exposure to Adempas and its active main metabolite (see PHARMACOLOGY, Pharmacokinetic Properties). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration. Additionally, kidney function during treatment with Adempas should be regularly checked in patients with renal impairment.

Adempas has not been sufficiently studied in patients with pulmonary hypertension who have a creatinine clearance below <30 mL/min (Stage 4 CKD). Patients with creatinine clearance <15 mL/min or on dialysis (Stage 5 CKD) have not been studied and therefore use of Adempas is not recommended in these patients (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Adempas has not been studied in patients with severe hepatic impairment (Child Pugh C); moderate hepatic impairment results in increased exposure. Adempas is not recommended for use in patients with severe hepatic impairment and should be used with caution in patients with moderate hepatic impairment.

Effects on Fertility

No specific studies with Adempas in humans have been conducted to evaluate effects on fertility. No effects on fertility were seen in a study on male and female rats at a relative exposure (unbound AUC) of approximately 5 to 7-fold higher than observed in patients with pulmonary hypertension.

Use in Pregnancy

Pregnancy Category X

Adempas has not been studied in pregnant women. Studies in animals have shown reproductive toxicity. Adempas was teratogenic in rats. Therefore, Adempas is contraindicated during pregnancy (see CONTRAINDICATIONS). Women of childbearing potential have to use effective contraception during treatment with Adempas.

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Women with childbearing potential must use two reliable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas.

If there is any doubt about risk to the foetus or what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk of harm to the foetus.

No specific studies on riociguat in semen have been conducted. It has been shown in the quantitative autoradiography that riociguat-related radioactivity was in the testes and in the accessory sex glands. Thus it can be assumed that it is in the semen. Riociguat is non-genotoxic (see Genotoxicity), thus no effect on DNA of sperm is expected.

Developmental toxicity studies in rats and rabbits have shown reproductive toxicity of riociguat. In rats, an increased rate of cardiac malformation was observed as well as a reduced gestation rate due to early resorption at maternal systemic exposure of about 7-times the maximum anticipated human exposure (MAHE; based on 2.5 mg three times daily), with an NOAEL at ~2 times MAHE. In rabbits, abortion and foetal toxicity were seen starting at systemic exposure of about 3-times MAHE, with an NOAEL similar to the MAHE.

Use in Lactation

No data on the use of Adempas in breastfeeding women are available. Data from animals indicate that riociguat is secreted into milk.

Because of the potential for serious adverse reactions in nursing infants, Adempas is contraindicated during breastfeeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the importance of the medicine for the mother.

Paediatric Use

The safety and efficacy of Adempas have not yet been studied in patients below 18 years. No data are available. Therefore, Adempas is not recommended in paediatrics. In fast growing adolescent rats effects on bone formation (i.e. an increase in overall bone mass) were seen. No such effects were observed after administration of riociguat to adult rats.

Use in the Elderly

Of the total number of subjects in the Phase III clinical program, 23% were 65 and over, and 6% were 75 and over. The incidence of hypotension in patients between 65 and 75 treated with Adempas was 16.4%, versus 5.2% for the placebo group. The incidence of hypotension in patients 75 years and older treated with Adempas was 15.9%, versus 0.0% in the placebo group. The incidence of hypotension in patients < 65 was 7.1% in the Adempas-treated group, versus 3.4% in the placebo group. Particular care should be exercised during individual dose titration in elderly patients.

Genotoxicity

Riociguat showed no genotoxicity potential in bacterial mutagenicity tests, chromosomal aberration assays in Chinese hamster cells or in an *in vivo* mouse micronucleus assay.

Carcinogenicity

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

In the carcinogenicity study in mice, at exposure levels close to the human therapeutic exposure, impaired gastrointestinal motility, dysbiosis and chronic inflammation followed by mucosal degeneration and reactive hyperplasia as well as a statistically non-significant increase in intestinal tumours were seen. This sequence of events is a typical reaction in mice to a stimulus like inflammation or degeneration and therefore these tumours are not considered as relevant for humans.

Effect on Laboratory Tests

In the Phase III studies with Adempas in patients with CTEPH and PAH, mean changes in laboratory tests from baseline to end of study were clinically insignificant for the majority of the chemistry parameters tested.

Effects on Ability to Drive or Use Machines

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

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic Interactions

Effects of Other Substances on Adempas

Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP2C8, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of the unchanged drug, and renal excretion of the unchanged drug via glomerular filtration. 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.

In vitro, ketoconazole, classified as a strong CYP3A4 and P-gp inhibitor, has been shown to be a 'multi-pathway CYP and P-gp/BCRP inhibitor' for riociguat metabolism and excretion. Concomitant administration of ketoconazole 400 mg once daily 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.

Therefore concomitant use with strong multi-pathway CYP and P-gp/BCRP inhibitors, such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended (see PRECAUTIONS, Concomitant Use with Other Medicinal Products).

Medicines strongly inhibiting P-gp/BCRP such as the immunosuppressive agent cyclosporin, should be used with caution *(*see PRECAUTIONS, Concomitant Use with Other Medicinal Products*)*.

From the recombinant CYP isoforms investigated *in vitro*, CYP1A1 most effectively catalysed formation of the 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 (see PHARMACOLOGY, Pharmacokinetic Properties) could result in increased riociguat exposure, especially in smokers. Therefore, strong CYP1A1 inhibitors should be used with caution (see PRECAUTIONS, Concomitant Use with Other Medicinal Products).

Co-administration of clarithromycin (500 mg twice daily), classified as a strong and selective CYP3A4 inhibitor and also reported to be a weak-to-moderate P-gp inhibitor, increased riociguat mean AUC by 41% without significant change in C_{max}.

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

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%. This is not considered clinically relevant.

Co-administration of the antacid aluminium 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.

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 (see INDICATIONS and CLINICAL TRIALS, Treatment of Pulmonary Arterial Hypertension).

The concomitant use of Adempas with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to decreased riociguat plasma concentration.

Effects of Adempas on Other Substances

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

Lack of mutual pharmacokinetic interactions between riociguat and the CYP3A4 probe substrate midazolam was demonstrated *in vivo*.

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.

Pharmacodynamic Interactions

Nitrates

Adempas 2.5 mg tablets potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after Adempas. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see CONTRAINDICATIONS).

PDE inhibitors

Riociguat and PDE-5-inhibitors are modulators of intra-cellular cGMP through different modes of action, but both act as vasodilators clinically. When cGMP is elevated by combining both principles, an additive effect on systemic blood pressure is anticipated (see CONTRAINDICATIONS).

Preclinical studies in animal models showed additive systemic blood pressure lowering effect when riociguat was combined with either sildenafil or vardenafil. With increased doses, over additive effects on systemic blood pressure were observed in some cases.

In some patients, concomitant use of these two medicine classes can lower blood pressure significantly leading to symptomatic hypotension (see CONTRAINDICATIONS).

In an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) and single doses of riociguat (0.5 mg and 1 mg sequentially) showed additive haemodynamic effects. Doses above 1 mg riociguat 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 riociguat (1.0 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 riociguat resulted in a high rate of discontinuation, predominately due to hypotension. There was no evidence of a favourable clinical effect of the combination in the population studied.

Concomitant administration of Adempas with PDE-5-inhibitors (such as sildenafil, tadalafil, vardenafil) or non-specific PDE inhibitors (such as dypyridamole or theophylline) is contraindicated (see CONTRAINDICATIONS).

Warfarin / Phenprocoumon

Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of Adempas with other coumarin-derivates (e.g. 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*.

Acetylsalicylic Acid

Adempas neither potentiated the bleeding time caused by acetylsalicylic acid nor affected the platelet aggregation in humans.

ADVERSE EFFECTS

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

The safety profile of Adempas in CTEPH and PAH appeared to be similar, therefore adverse drug reactions (ADRs) identified from placebo controlled 12 and 16 week clinical trials are presented as pooled frequency in the table listed below (see Table 10).

Most of the undesirable effects are caused by relaxation of smooth muscle cells in the vasculature or gastrointestinal tract.

The most commonly reported adverse reactions, occurring in ≥ 10% of patients on Adempas treatment (up to 2.5 mg TDS), were headache, dizziness, dyspepsia, peripheral oedema, nausea, diarrhoea and vomiting.

With longer observation in uncontrolled long term extension studies, the safety profile was similar to that observed in the placebo-controlled Phase III trials.

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see PRECAUTIONS, Bleeding).

The overall rates of discontinuation due to an adverse event (AE) in the pivotal placebo controlled trials were low in all treatment arms (Pooled data: 2.9% for Adempas and 5.1% for placebo).The adverse events observed with Adempas at a cut-off of 5% are represented in

Table 9. Adverse drug reactions at a cut-off of 1% are listed in Table 10 below, they are classified according to System Organ Class (MedDRA version 15.0). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Table 9 All treatment-emergent adverse events reported in ≥ 5% patients in Phase III studies (pooled CHEST-1 and PATENT-1 data)

MedDRA Preferred term	Placebo % (n = 214)	Adempas % (n = 490)
Headache	17.3%	26.9%
Dizziness	12.1%	19.2%
Dyspepsia	7.9%	17.8%
Oedema peripheral	15.0%	17.3%
Nausea	10.7%	14.1%
Nasopharyngitis	10.3%	11.8%
Diarrhoea	7.9%	11.8%
Vomiting	6.5%	10.2%
Hypotension	2.8%	8.8%
Palpitations	4.7%	6.3%
Chest pain	7.0%	5.9%
Anaemia	1.9%	5.7%
Dyspnoea	12.1%	5.7%
Gastrooesophageal reflux disease	1.9%	5.1%
Cough	13.6%	4.9%
Chest discomfort	5.6%	3.1%
Pain in extremity	5.1%	2.9%
Fatigue	5.6%	2.4%

Table 10 All treatment-emergent adverse drug reactions reported in ≥ 1% patients in Phase III studies (pooled CHEST-1 and PATENT-1 data)

System Organ Class (MedDRA)	MedDRA labeling grouping (Preferred term)	Placebo % (n = 214)	Adempas % (n = 490)
Infections and Infestations	Gastroenteritis	0.9%	2.4%
Blood and lymphatic system disorders	Anaemia (incl. respective laboratory parameters)	2.3%	6.7%
Nervous system disorders	Headache	17.8%	26.9%
	Dizziness	13.1%	19.8%
Cardiac disorders	Palpitations	4.7%	6.3%
Vascular disorders	Hypotension	3.7%	9.8%

System Organ Class (MedDRA)	MedDRA labeling grouping (Preferred term)	Placebo % (n = 214)	Adempas % (n = 490)
Respiratory, thoracic and mediastinal disorders	Nasal congestion	2.8%	4.3%
	Epistaxis	1.4%	2.9%
	Haemoptysis	0.9%	2.0%
Gastrointestinal disorders	Dyspepsia	8.4%	18.6%
	Nausea	10.7%	14.1%
	Diarrhoea	7.9%	12.0%
	Vomiting	6.5%	10.2%
	Gastrointestinal and abdominal pains	7.0%	9.4%
	Gastrooesophageal reflux disease	1.9%	5.1%
	Constipation	1.4%	4.5%
	Gastritis	0%	2.9%
	Dysphagia	0%	2.2%
	Abdominal distension	0.5%	2.0%
General disorders and administration site conditions	Oedema peripheral	15.0%	17.3%

Less frequent Adverse Drug Reactions < 1% in the Phase III studies:

Respiratory, thoracic and mediastinal disorders: pulmonary haemorrhage*

* fatal pulmonary haemorrhage was reported in uncontrolled long term extension studies

Abnormal Haematologic and Clinical Chemistry Findings

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

In a pooled analysis of placebo-controlled Phase III studies in subjects with CTEPH or PAH, changes from baseline in mean haemoglobin (-0.58 g/dL vs. 0.13 g/dL) and haematocrit (-1.66% vs. 0.45%) were observed in patients receiving Adempas or placebo, respectively. Decreases in haemoglobin (24.1% vs. 9.1%) and haematocrit (13.3% vs. 4.9%) were observed in patients receiving Adempas and placebo, respectively. Anaemia 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.

DOSAGE AND ADMINISTRATION

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

Tablets should be taken three times daily approximately 6 to 8 hours apart. Adempas can be taken with or without food.

Antacids, if required, should be taken at least 1 hour after Adempas (see INTERACTIONS WITH OTHER MEDICINES, Pharmacokinetic Interactions).

Adults

Treatment Initiation

The recommended starting dose is 1.0 mg three times daily for 2 weeks. For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day. Dosage should be increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥ 95 mmHg and the patient has no signs or symptoms of hypotension. During the up-titration phase:

- if systolic blood pressure is ≥ 95 mmHg and the patient has signs or symptoms of hypotension, the dosage should be decreased by 0.5 mg TDS
- if systolic blood pressure is < 95 mmHg and the patient has no signs or symptoms of hypotension, the dosage should be maintained
- if systolic blood pressure is < 95 mmHg and the patient has signs or symptoms of hypotension, the dosage should be decreased by 0.5 mg TDS

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

If at any time, the patient has symptoms of hypotension, decrease the dosage by 0.5 mg taken three times a day.

Treatment Discontinuation

In case treatment has to be interrupted for 3 days or more, restart treatment at 1 mg three times daily for 2 weeks, and continue treatment with the dose titration regimen as described above.

Special Populations

Individual dose titration at treatment initiation allows to adjust the dose to the patient's needs.

Paediatric Use

The safety and efficacy of Adempas have not yet been studied in patients below 18 years. No data are available. Therefore, Adempas is not recommended for use in paediatric patients.

Use in the Elderly

In elderly patients (≥ 65 years) particular care should be exercised during individual dose titration (see PHARMACOLOGY, Pharmacokinetic Properties).

Hepatic Impairment

Patients (non-smokers) with mild hepatic impairment (Child Pugh A) had an increased exposure of riociguat by 35% compared to healthy controls which is within the day to day variability. Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to Adempas (see PHARMACOLOGY, Pharmacokinetic Properties). Particular care should be exercised during individual dose titration.

Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is not recommended in these patients (see PRECAUTIONS, Hepatic Impairment).

Renal Impairment

Patients with mild (Stage 2 CKD), moderate (Stage 3 CKD) or severe (Stage 4 CKD) renal impairment (creatinine clearance 80 – 15 mL/min) showed a higher exposure to Adempas (see PHARMACOLOGY, Pharmacokinetic Properties). Particular care should be exercised during individual dose titration.

Patients with creatinine clearance < 15 mL/min or on dialysis (Stage 5) have not been studied and therefore use of Adempas is not recommended in these patients (see PRECAUTIONS, Renal Impairment).

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 PRECAUTIOINS, Additional Information on Special Populations).

Pregnancy

Adempas is contraindicated during pregnancy (see CONTRAINDICATIONS). Women of child-bearing potential should be tested for pregnancy prior to initiating treatment, at regular intervals during treatment and one month after discontinuation of treatment with Adempas.

OVERDOSAGE

Inadvertent overdosing with total daily doses of Adempas 9 – 25 mg for periods 2 – 32 days has been reported. Adverse reactions were similar to those seen at lower doses (see ADVERSE EFFECTS).

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 dialysable.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Adempas 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets in polypropylene / aluminium blister packs: 21, 42 and 84 tablet packs (not all pack sizes may be marketed).

Adempas 0.5 mg film-coated tablets: White, round, biconvex tablets marked with the Bayer cross on one side and 0.5 and an “R” on the other side.

Adempas 1 mg film-coated tablets: Pale yellow, round, biconvex tablets marked with the Bayer cross on one side and 1 and an “R” on the other side.

Adempas 1.5 mg film-coated tablets: Yellow orange, round, biconvex tablets marked with the Bayer cross on one side and 1.5 and an “R” on the other side.

Adempas 2 mg film-coated tablets: Pale orange, round, biconvex tablets marked with the Bayer cross on one side and 2 and an “R” on the other side.

Adempas 2.5 mg film-coated tablets: Red orange, round, biconvex tablets marked with the Bayer cross on one side and 2.5 and an “R” on the other side.

Storage Conditions

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd

ABN 22 000 138 714

875 Pacific Highway

Pymble NSW 2073

Bayer Medical Information and Drug safety: 1800 673 270 (Toll free)

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG:

14 April 2014

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