ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg of riociguat.

Excipients with known effect:

Each film-coated tablet contains 37.8 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 0.5 and an “R” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

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

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2).

Dose should be increased by 0.5 mg three times daily every two weeks 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. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1). If systolic blood pressure falls below 95 mmHg, the dose 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 current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (see section 5.2).

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 adjustment of the dose to the patient´s needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone (see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is contraindicated in these patients (see section 4.3). Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients (see section 4.4).

Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2).
A dose decrease may be required in patients who stop smoking.

Method of administration

For oral use.

4.3 Contraindications

- Co-administration with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see section 4.5)
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see section 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).
In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.
The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.
Serious bleeding occurred in 2.4% (12 /490) of patients taking riociguat compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking riociguat compared to 0/214 patients taking placebo, 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.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).
Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients (see section 5.2). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients (see section 4.3). PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B) (see section 5.2). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat (see sections 4.2 and 5.2).

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see section 4.5 and 5.2).
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see section 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone

(see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

Information about excipients

Each 0.5 mg film coated tablet contains 37.8 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see section 4.3).

PDE 5 inhibitors
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 an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) 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 to 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part of this study (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 use of riociguat with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.3).

Warfarin/phenprocoumon
Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other cumarin-derivatives (e.g. phenprocoumon) is also not expected to alter prothrombin time.
Lack of pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetylsalicylic acid
Riociguat did not potentiate the bleeding time caused by acetyl-salicylic acid or affect the platelet aggregation in humans.

Effects of other substances on riociguat

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

In vitro, ketoconazole, classified as a 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 (see section 5.2). 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.

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 section 4.4).

Drugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive cyclosporine A, should be used with caution (see sections 4.4 and 5.2).

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: 1/10th to 1/3rd of riociguat).

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 catalysed formation of riociguat's main metabolite most effectively. 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 (see section 5.2). Strong CYP1A1 inhibitors should be used with caution (see section 4.4).

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.

Co-administration of the antacid aluminium hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see section 4.2). Antacids should be taken at least 2 hours before, or 1 hour after riociguat.

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1).

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

Smoking
In cigarette smokers riociguat exposure is reduced by 50-60% (see section 5.2). Therefore, patients are advised to stop smoking (see section 4.2).

Effects of riociguat on other substances

Riociguat and its main metabolite are not inhibitors or inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations. Riociguat and its main metabolite are 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer (see section 5.3). Therefore, Adempas is contraindicated during pregnancy (see section 4.3). Monthly pregnancy tests are recommended.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Adempas.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with this medicine.

Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, decreased testes weights were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicine, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1).

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

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

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see section 4.4).

The safety profile of Adempas in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with Adempas are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with Adempas in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Epistaxis Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhoea Nausea Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,
ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system 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 is associated with endothelial dysfunction, impaired synthesis of NO 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 independently of NO.
Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.
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 efficacy and safety

Efficacy in patients with CTEPH

A randomised, double-blind, multi-national, placebo controlled, phase III study (CHEST-1) was conducted in 261 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (72%) or persistent or recurrent CTEPH after pulmonary endarterectomy (PEA; 28%). During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily) which was then maintained for a further 8 weeks. The primary endpoint of the study was the placebo adjusted change from baseline in 6-minute walk distance (6MWD) at the last visit (week 16).
At the last visit, the increase in 6MWD in patients treated with riociguat was 46 m (95% confidence interval (CI): 25 m to 67 m; $p<0.0001$), compared to placebo. Results were consistent in the main sub-groups evaluated (ITT analysis, see table 2).

Table 2: Effects of riociguat on 6MWD in CHEST-1 at last visit

Entire patient population	**Riociguat (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Mean change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-adjusted difference (m) 95% CI, [p-value]	46 25 to 67 [<0.0001]	
FC III patient population	**Riociguat (n=107)**	**Placebo (n=60)**
Baseline (m) [SD]	326 [81]	345 [73]
Mean change from baseline (m) [SD]	38 [75]	-17 [95]
Placebo-adjusted difference (m) 95% CI	56 29 to 83	
FC II patient population	**Riociguat (n=55)**	**Placebo (n=25)**
Baseline (m) [SD]	387 [59]	386 [64]
Mean change from baseline (m) [SD]	45 [82]	20 [51]
Placebo-adjusted difference (m) 95% CI	25 -10 to 61	
Inoperable patient population	**Riociguat (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Mean change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-adjusted difference (m) 95% CI	54 29 to 79	
Patient population with CTEPH post-PEA	**Riociguat (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Mean change from baseline (m) [SD]	27 [68]	1.8 [73]
Placebo- adjusted mean LS-difference (m) 95% CI	27 -10 to 63	

LS=least squares

Improvement in exercise capacity was accompanied by improvement in multiple clinically relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters.

Table 3: Effects of riociguat in CHEST-1 on PVR, NT-proBNP and WHO functional class at last visit

PVR	**Riociguat (n=151)**	**Placebo (n=82)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-246.4 –303.3 to –189.5 [<0.0001]	
NT-proBNP	**Riociguat (n=150)**	**Placebo (n=73)**
Baseline (ng/L) [SD]	1508.3 [2337.8]	1705.8 [2567.2]
Mean change from baseline (ng/L) [SD]	-290.7 [1716.9]	76.4 [1446.6]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-444.0 -843.0 to -45.0 [<0.0001]	
Change in WHO Functional Class	**Riociguat (n=173)**	**Placebo (n=87)**
Improved	57 (32.9%)	13 (14.9%)
Stable	107 (61.8%)	68 (78.2%)
Deteriorated	9 (5.2%)	6 (6.9%)
p-value	0.0026	

PVR= pulmonary vascular resistance

NT-proBNP =N-terminal prohormone of brain natriuretic peptide

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat IDT 1.0-2.5 mg, 2.9%; placebo, 2.3%).

Long-term treatment

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily.
The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group.

The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.

Efficacy in patients with PAH

A randomised, double-blind, multi-national, placebo controlled, phase III study (PATENT-1) was conducted in 443 adult patients with PAH (riociguat individual dose titration up to 2.5 mg three times daily: n=254, placebo: n=126, riociguat “capped” dose titration (CT) up to 1.5 mg (exploratory dose arm, no statistical testing performed; n=63)). Patients were either treatment-naïve (50%) or pre-treated with an endothelin receptor antagonist (ERA; 43%) or a prostacyclin analogue (inhaled (iloprost), oral (beraprost) or subcutaneous (treprostinil); 7%) and had been diagnosed with idiopathic or heritable PAH (63.4%), PAH associated with connective tissue disease (25.1%) and congenital heart disease (7.9%).
During the first 8 weeks riociguat was titrated every 2-weeks based on the patient’s systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg

three times daily), which was then maintained for a further 4 weeks. The primary endpoint of the study was placebo-adjusted change from baseline in 6MWD at the last visit (week 12).

At the last visit the increase in 6MWD with riociguat individual dose titration (IDT) was 36 m (95% CI: 20 m to 52 m; $p<0.0001$) compared to placebo. Treatment-naïve patients (n=189) improved by 38 m, and pre-treated patients (n=191) by 36 m (ITT analysis, see table 4). Further exploratory subgroup analysis revealed a treatment effect of 26 m, (95% CI: 5 m to 46 m) in patients pre-treated with ERAs (n=167) and a treatment effect of 101 m (95% CI: 27 m to 176 m) in patients pre-treated with prostacyclin analogues (n=27).

Table 4: Effects of riociguat on 6MWD in PATENT-1 at last visit

Entire patient population	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Baseline (m) [SD]	361 [68]	368 [75]	363 [67]
Mean change from baseline (m) [SD]	30 [66]	-6 [86]	31 [79]
Placebo-adjusted difference (m) 95% CI, [p-value]	36 20 to 52 [<0.0001]		
FC III patients	**Riociguat IDT (n=140)**	**Placebo (n=58)**	**Riociguat CT (n=39)**
Baseline (m) [SD]	338 [70]	347 [78]	351 [68]
Mean change from baseline (m) [SD]	31 [64]	-27 [98]	29 [94]
Placebo-adjusted difference (m) 95% CI	58 35 to 81		
FC II patients	**Riociguat IDT (n=108)**	**Placebo (n=60)**	**Riociguat CT (n=19)**
Baseline (m) [SD]	392 [51]	393 [61]	378 [64]
Mean change from baseline (m) [SD]	29 [69]	19 [63]	43 [50]
Placebo-adjusted difference (m) 95% CI	10 -11 to 31		
Treatment-naïve patient population	**Riociguat IDT (n=123)**	**Placebo (n=66)**	**Riociguat CT (n=32)**
Baseline (m) [SD]	370 [66]	360 [80]	347 [72]
Mean change from baseline (m) [SD]	32 [74]	-6 [88]	49 [47]
Placebo-adjusted difference (m) 95% CI	38 14 to 62		
Pre-treated patient population	**Riociguat IDT (n=131)**	**Placebo (n=60)**	**Riociguat CT (n=31)**
Baseline (m) [SD]	353 [69]	376 [68]	380 [57]
Mean change from baseline (m) [SD]	27 [58]	-5 [83]	12 [100]
Placebo- adjusted difference (m) 95% CI	36 15 to 56		

Improvement in exercise capacity was accompanied by consistent improvement in multiple clinically-relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters (see table 5).

Table 5: Effects of riociguat in PATENT-1 on PVR and NT-proBNP at last visit

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm-5) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	1026.7 [1799.2]	1228.1 [1774.9]	1189.7 [1404.7]
Mean change from baseline (ng/L) [SD]	-197.9 [1721.3]	232.4 [1011.1]	-471.5 [913.0]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-431.8 (-781.5 to -82.1) [<0.0001]		
Change in WHO Functional Class	**Riociguat IDT (n = 254)**	**Placebo (n = 125)**	**Riociguat CT (n=63)**
Improved	53 (20.9%)	18 (14.4%)	15 (23.8%)
Stable	192 (75.6%)	89 (71.2%)	43 (68.3%)
Deteriorated	9 (3.6%)	18 (14.4%)	5 (7.9%)
p-value	0.0033		

Riociguat-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test) (see table 6).

Table 6: Effects of riociguat in PATENT-1 on events of clinical worsening

Clinical Worsening Events	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Patients with any clinical worsening	3 (1.2%)	8 (6.3%)	2 (3.2%)
Death	2 (0.8%)	3 (2.4%)	1 (1.6%)
Hospitalisations due to PH	1 (0.4%)	4 (3.2%)	0
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)	1 (1.6%)
Persistent worsening of Functional Class due to PH	0	1 (0.8%)	0
Start of new PH treatment	1 (0.4%)	5 (4.0%)	1 (1.6%)

Patients treated with riociguat showed significant improvement in Borg CR 10 dyspnoea score (mean change from baseline (SD): riociguat -0.4 (2), placebo 0.1 (2); p = 0.0022).

Adverse Events leading to discontinuation occurred less frequently in both riociguat treatment groups than in the placebo group (riociguat IDT 1.0-2.5 mg, 3.1%; riociguat CT 1.6%; placebo, 7.1%).

Long-term treatment

An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.

The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adempas in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.
See section 4.2 for information on paediatric use.

5.2 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 reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-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 M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.
CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found 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 12 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%.

Special populations

Gender
Pharmacokinetic data reveal no relevant differences due to gender in the exposure to riociguat.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients.

Elderly population
Elderly patients (65 years or older) 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.

Inter-ethnic differences
Pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
Pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

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. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).

Patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied (see section 4.4).

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 (creatinine clearance 80-50 mL/min), moderate (creatinine clearance <50-30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively.
Data in patients with creatinine clearance <30 mL/min are limited and there are no data for patients on dialysis.
Due to the high plasma protein binding riociguat is not expected to be dialysable.

5.3 Preclinical safety data

Non-clinical data revealed no specific hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity and carcinogenicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of riociguat (haemodynamic and smooth muscle relaxing effects).

In growing, juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats.

In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. Moderate passage across the placental barrier was observed. 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-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cellulose microcrystalline
crospovidone
hypromellose
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose
propylene glycol
titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.
Pack sizes: 42, 84 or 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/001
EU/1/13/907/002
EU/1/13/907/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Adempas 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of riociguat.

Excipients with known effect:

Each film-coated tablet contains 37.2 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1 and an "R" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

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

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2).

Dose should be increased by 0.5 mg three times daily every two weeks 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. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1). If systolic blood pressure falls below 95 mmHg, the dose 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 current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (see section 5.2).

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 adjustment of the dose to the patient´s needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone (see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is contraindicated in these patients (see section 4.3). Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients (see section 4.4).

Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2).
A dose decrease may be required in patients who stop smoking.

Method of administration

For oral use.

4.3 Contraindications

- Co-administration with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see section 4.5)
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see section 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).
In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.
The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.
Serious bleeding occurred in 2.4% (12 /490) of patients taking riociguat compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking riociguat compared to 0/214 patients taking placebo, 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.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).
Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients (see section 5.2). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients (see section 4.3). PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B) (see section 5.2). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat (see sections 4.2 and 5.2).

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see section 4.5 and 5.2).
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see section 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone

(see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

Information about excipients

Each 1 mg film coated tablet contains 37.2 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see section 4.3).

PDE 5 inhibitors
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 an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) 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 to 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part of this study (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 use of riociguat with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.3).

Warfarin/phenprocoumon
Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other cumarin-derivatives (e.g. phenprocoumon) is also not expected to alter prothrombin time.
Lack of pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetylsalicylic acid
Riociguat did not potentiate the bleeding time caused by acetyl-salicylic acid or affect the platelet aggregation in humans.

Effects of other substances on riociguat

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

In vitro, ketoconazole, classified as a 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 (see section 5.2). 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.

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 section 4.4).

Drugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive cyclosporine A, should be used with caution (see sections 4.4 and 5.2).

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: 1/10th to 1/3rd of riociguat).

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 catalysed formation of riociguat's main metabolite most effectively. 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 (see section 5.2). Strong CYP1A1 inhibitors should be used with caution (see section 4.4).

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.

Co-administration of the antacid aluminium hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see section 4.2). Antacids should be taken at least 2 hours before, or 1 hour after riociguat.

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1).

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

Smoking
In cigarette smokers riociguat exposure is reduced by 50-60% (see section 5.2). Therefore, patients are advised to stop smoking (see section 4.2).

Effects of riociguat on other substances

Riociguat and its main metabolite are not inhibitors or inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations. Riociguat and its main metabolite are 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer (see section 5.3). Therefore, Adempas is contraindicated during pregnancy (see section 4.3). Monthly pregnancy tests are recommended.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Adempas.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with this medicine.

Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, decreased testes weights were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicine, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1).

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

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

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see section 4.4).

The safety profile of Adempas in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with Adempas are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with Adempas in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Epistaxis Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhoea Nausea Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,
ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system 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 is associated with endothelial dysfunction, impaired synthesis of NO 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 independently of NO.
Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.
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 efficacy and safety

Efficacy in patients with CTEPH

A randomised, double-blind, multi-national, placebo controlled, phase III study (CHEST-1) was conducted in 261 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (72%) or persistent or recurrent CTEPH after pulmonary endarterectomy (PEA; 28%). During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily) which was then maintained for a further 8 weeks. The primary endpoint of the study was the placebo adjusted change from baseline in 6-minute walk distance (6MWD) at the last visit (week 16).
At the last visit, the increase in 6MWD in patients treated with riociguat was 46 m (95% confidence interval (CI): 25 m to 67 m; $p<0.0001$), compared to placebo. Results were consistent in the main sub-groups evaluated (ITT analysis, see table 2).

Table 2: Effects of riociguat on 6MWD in CHEST-1 at last visit

Entire patient population	**Riociguat (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Mean change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-adjusted difference (m) 95% CI, [p-value]	46 25 to 67 [<0.0001]	
FC III patient population	**Riociguat (n=107)**	**Placebo (n=60)**
Baseline (m) [SD]	326 [81]	345 [73]
Mean change from baseline (m) [SD]	38 [75]	-17 [95]
Placebo-adjusted difference (m) 95% CI	56 29 to 83	
FC II patient population	**Riociguat (n=55)**	**Placebo (n=25)**
Baseline (m) [SD]	387 [59]	386 [64]
Mean change from baseline (m) [SD]	45 [82]	20 [51]
Placebo-adjusted difference (m) 95% CI	25 -10 to 61	
Inoperable patient population	**Riociguat (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Mean change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-adjusted difference (m) 95% CI	54 29 to 79	
Patient population with CTEPH post-PEA	**Riociguat (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Mean change from baseline (m) [SD]	27 [68]	1.8 [73]
Placebo- adjusted mean LS-difference (m) 95% CI	27 -10 to 63	

LS=least squares

Improvement in exercise capacity was accompanied by improvement in multiple clinically relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters.

Table 3: Effects of riociguat in CHEST-1 on PVR, NT-proBNP and WHO functional class at last visit

PVR	**Riociguat (n=151)**	**Placebo (n=82)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-246.4 –303.3 to –189.5 [<0.0001]	
NT-proBNP	**Riociguat (n=150)**	**Placebo (n=73)**
Baseline (ng/L) [SD]	1508.3 [2337.8]	1705.8 [2567.2]
Mean change from baseline (ng/L) [SD]	-290.7 [1716.9]	76.4 [1446.6]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-444.0 -843.0 to -45.0 [<0.0001]	
Change in WHO Functional Class	**Riociguat (n=173)**	**Placebo (n=87)**
Improved	57 (32.9%)	13 (14.9%)
Stable	107 (61.8%)	68 (78.2%)
Deteriorated	9 (5.2%)	6 (6.9%)
p-value	0.0026	

PVR= pulmonary vascular resistance

NT-proBNP =N-terminal prohormone of brain natriuretic peptide

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat IDT 1.0-2.5 mg, 2.9%; placebo, 2.3%).

Long-term treatment

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily.
The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group.

The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.

Efficacy in patients with PAH

A randomised, double-blind, multi-national, placebo controlled, phase III study (PATENT-1) was conducted in 443 adult patients with PAH (riociguat individual dose titration up to 2.5 mg three times daily: n=254, placebo: n=126, riociguat “capped” dose titration (CT) up to 1.5 mg (exploratory dose arm, no statistical testing performed; n=63)). Patients were either treatment-naïve (50%) or pre-treated with an endothelin receptor antagonist (ERA; 43%) or a prostacyclin analogue (inhaled (iloprost), oral (beraprost) or subcutaneous (treprostinil); 7%) and had been diagnosed with idiopathic or heritable PAH (63.4%), PAH associated with connective tissue disease (25.1%) and congenital heart disease (7.9%).
During the first 8 weeks riociguat was titrated every 2-weeks based on the patient’s systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg

three times daily), which was then maintained for a further 4 weeks. The primary endpoint of the study was placebo-adjusted change from baseline in 6MWD at the last visit (week 12).

At the last visit the increase in 6MWD with riociguat individual dose titration (IDT) was 36 m (95% CI: 20 m to 52 m; $p<0.0001$) compared to placebo. Treatment-naïve patients (n=189) improved by 38 m, and pre-treated patients (n=191) by 36 m (ITT analysis, see table 4). Further exploratory subgroup analysis revealed a treatment effect of 26 m, (95% CI: 5 m to 46 m) in patients pre-treated with ERAs (n=167) and a treatment effect of 101 m (95% CI: 27 m to 176 m) in patients pre-treated with prostacyclin analogues (n=27).

Table 4: Effects of riociguat on 6MWD in PATENT-1 at last visit

Entire patient population	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Baseline (m) [SD]	361 [68]	368 [75]	363 [67]
Mean change from baseline (m) [SD]	30 [66]	-6 [86]	31 [79]
Placebo-adjusted difference (m) 95% CI, [p-value]	36 20 to 52 [<0.0001]		
FC III patients	**Riociguat IDT (n=140)**	**Placebo (n=58)**	**Riociguat CT (n=39)**
Baseline (m) [SD]	338 [70]	347 [78]	351 [68]
Mean change from baseline (m) [SD]	31 [64]	-27 [98]	29 [94]
Placebo-adjusted difference (m) 95% CI	58 35 to 81		
FC II patients	**Riociguat IDT (n=108)**	**Placebo (n=60)**	**Riociguat CT (n=19)**
Baseline (m) [SD]	392 [51]	393 [61]	378 [64]
Mean change from baseline (m) [SD]	29 [69]	19 [63]	43 [50]
Placebo-adjusted difference (m) 95% CI	10 -11 to 31		
Treatment-naïve patient population	**Riociguat IDT (n=123)**	**Placebo (n=66)**	**Riociguat CT (n=32)**
Baseline (m) [SD]	370 [66]	360 [80]	347 [72]
Mean change from baseline (m) [SD]	32 [74]	-6 [88]	49 [47]
Placebo-adjusted difference (m) 95% CI	38 14 to 62		
Pre-treated patient population	**Riociguat IDT (n=131)**	**Placebo (n=60)**	**Riociguat CT (n=31)**
Baseline (m) [SD]	353 [69]	376 [68]	380 [57]
Mean change from baseline (m) [SD]	27 [58]	-5 [83]	12 [100]
Placebo- adjusted difference (m) 95% CI	36 15 to 56		

Improvement in exercise capacity was accompanied by consistent improvement in multiple clinically-relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters (see table 5).

Table 5: Effects of riociguat in PATENT-1 on PVR and NT-proBNP at last visit

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm-5) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	1026.7 [1799.2]	1228.1 [1774.9]	1189.7 [1404.7]
Mean change from baseline (ng/L) [SD]	-197.9 [1721.3]	232.4 [1011.1]	-471.5 [913.0]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-431.8 (-781.5 to -82.1) [<0.0001]		
Change in WHO Functional Class	**Riociguat IDT (n = 254)**	**Placebo (n = 125)**	**Riociguat CT (n=63)**
Improved	53 (20.9%)	18 (14.4%)	15 (23.8%)
Stable	192 (75.6%)	89 (71.2%)	43 (68.3%)
Deteriorated	9 (3.6%)	18 (14.4%)	5 (7.9%)
p-value	0.0033		

Riociguat-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test) (see table 6).

Table 6: Effects of riociguat in PATENT-1 on events of clinical worsening

Clinical Worsening Events	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Patients with any clinical worsening	3 (1.2%)	8 (6.3%)	2 (3.2%)
Death	2 (0.8%)	3 (2.4%)	1 (1.6%)
Hospitalisations due to PH	1 (0.4%)	4 (3.2%)	0
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)	1 (1.6%)
Persistent worsening of Functional Class due to PH	0	1 (0.8%)	0
Start of new PH treatment	1 (0.4%)	5 (4.0%)	1 (1.6%)

Patients treated with riociguat showed significant improvement in Borg CR 10 dyspnoea score (mean change from baseline (SD): riociguat -0.4 (2), placebo 0.1 (2); p = 0.0022).

Adverse Events leading to discontinuation occurred less frequently in both riociguat treatment groups than in the placebo group (riociguat IDT 1.0-2.5 mg, 3.1%; riociguat CT 1.6%; placebo, 7.1%).

Long-term treatment

An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.

The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adempas in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.
See section 4.2 for information on paediatric use.

5.2 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 reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-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 M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.
CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found 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 12 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%.

Special populations

Gender
Pharmacokinetic data reveal no relevant differences due to gender in the exposure to riociguat.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients.

Elderly population
Elderly patients (65 years or older) 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.

Inter-ethnic differences
Pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
Pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

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. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).

Patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied (see section 4.4).

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 (creatinine clearance 80-50 mL/min), moderate (creatinine clearance <50-30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively.
Data in patients with creatinine clearance <30 mL/min are limited and there are no data for patients on dialysis.
Due to the high plasma protein binding riociguat is not expected to be dialysable.

5.3 Preclinical safety data

Non-clinical data revealed no specific hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity and carcinogenicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of riociguat (haemodynamic and smooth muscle relaxing effects).

In growing, juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats.

In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. Moderate passage across the placental barrier was observed. 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-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cellulose microcrystalline
crospovidone
hypromellose
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose
propylene glycol
titanium dioxide (E 171)
ferric oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.
Pack sizes: 42, 84 or 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/004
EU/1/13/907/005
EU/1/13/907/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Adempas 1.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1.5 mg of riociguat.

Excipients with known effect:

Each film-coated tablet contains 36.8 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1.5 and an “R” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

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

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2).

Dose should be increased by 0.5 mg three times daily every two weeks 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. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1). If systolic blood pressure falls below 95 mmHg, the dose 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 current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (see section 5.2).

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 adjustment of the dose to the patient´s needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone (see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is contraindicated in these patients (see section 4.3). Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients (see section 4.4).

Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2).
A dose decrease may be required in patients who stop smoking.

Method of administration

For oral use.

4.3 Contraindications

- Co-administration with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see section 4.5)
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see section 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).
In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.
The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.
Serious bleeding occurred in 2.4% (12 /490) of patients taking riociguat compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking riociguat compared to 0/214 patients taking placebo, 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.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).
Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients (see section 5.2). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients (see section 4.3). PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B) (see section 5.2). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat (see sections 4.2 and 5.2).

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see section 4.5 and 5.2).
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see section 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone

(see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

Information about excipients

Each 1.5 mg film coated tablet contains 36.8 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see section 4.3).

PDE 5 inhibitors
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 an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) 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 to 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part of this study (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 use of riociguat with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.3).

Warfarin/phenprocoumon
Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other cumarin-derivatives (e.g. phenprocoumon) is also not expected to alter prothrombin time.
Lack of pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetylsalicylic acid
Riociguat did not potentiate the bleeding time caused by acetyl-salicylic acid or affect the platelet aggregation in humans.

Effects of other substances on riociguat

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

In vitro, ketoconazole, classified as a 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 (see section 5.2). 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.

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 section 4.4).

Drugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive cyclosporine A, should be used with caution (see sections 4.4 and 5.2).

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: $1/10^{th}$ to $1/3^{rd}$ of riociguat).

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 catalysed formation of riociguat's main metabolite most effectively. 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 (see section 5.2). Strong CYP1A1 inhibitors should be used with caution (see section 4.4).

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.

Co-administration of the antacid aluminium hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see section 4.2). Antacids should be taken at least 2 hours before, or 1 hour after riociguat.

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1).

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

Smoking
In cigarette smokers riociguat exposure is reduced by 50-60% (see section 5.2). Therefore, patients are advised to stop smoking (see section 4.2).

Effects of riociguat on other substances

Riociguat and its main metabolite are not inhibitors or inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations. Riociguat and its main metabolite are 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer (see section 5.3). Therefore, Adempas is contraindicated during pregnancy (see section 4.3). Monthly pregnancy tests are recommended.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Adempas.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with this medicine.

Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, decreased testes weights were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicine, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1).

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

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

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see section 4.4).

The safety profile of Adempas in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with Adempas are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with Adempas in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Epistaxis Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhoea Nausea Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,
ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system 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 is associated with endothelial dysfunction, impaired synthesis of NO 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 independently of NO.
Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.
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 efficacy and safety

Efficacy in patients with CTEPH

A randomised, double-blind, multi-national, placebo controlled, phase III study (CHEST-1) was conducted in 261 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (72%) or persistent or recurrent CTEPH after pulmonary endarterectomy (PEA; 28%). During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily) which was then maintained for a further 8 weeks. The primary endpoint of the study was the placebo adjusted change from baseline in 6-minute walk distance (6MWD) at the last visit (week 16).
At the last visit, the increase in 6MWD in patients treated with riociguat was 46 m (95% confidence interval (CI): 25 m to 67 m; $p<0.0001$), compared to placebo. Results were consistent in the main sub-groups evaluated (ITT analysis, see table 2).

Table 2: Effects of riociguat on 6MWD in CHEST-1 at last visit

Entire patient population	**Riociguat (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Mean change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-adjusted difference (m) 95% CI, [p-value]	46 25 to 67 [<0.0001]	
FC III patient population	**Riociguat (n=107)**	**Placebo (n=60)**
Baseline (m) [SD]	326 [81]	345 [73]
Mean change from baseline (m) [SD]	38 [75]	-17 [95]
Placebo-adjusted difference (m) 95% CI	56 29 to 83	
FC II patient population	**Riociguat (n=55)**	**Placebo (n=25)**
Baseline (m) [SD]	387 [59]	386 [64]
Mean change from baseline (m) [SD]	45 [82]	20 [51]
Placebo-adjusted difference (m) 95% CI	25 -10 to 61	
Inoperable patient population	**Riociguat (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Mean change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-adjusted difference (m) 95% CI	54 29 to 79	
Patient population with CTEPH post-PEA	**Riociguat (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Mean change from baseline (m) [SD]	27 [68]	1.8 [73]
Placebo- adjusted mean LS-difference (m) 95% CI	27 -10 to 63	

LS=least squares

Improvement in exercise capacity was accompanied by improvement in multiple clinically relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters.

Table 3: Effects of riociguat in CHEST-1 on PVR, NT-proBNP and WHO functional class at last visit

PVR	**Riociguat (n=151)**	**Placebo (n=82)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-246.4 –303.3 to –189.5 [<0.0001]	
NT-proBNP	**Riociguat (n=150)**	**Placebo (n=73)**
Baseline (ng/L) [SD]	1508.3 [2337.8]	1705.8 [2567.2]
Mean change from baseline (ng/L) [SD]	-290.7 [1716.9]	76.4 [1446.6]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-444.0 -843.0 to -45.0 [<0.0001]	
Change in WHO Functional Class	**Riociguat (n=173)**	**Placebo (n=87)**
Improved	57 (32.9%)	13 (14.9%)
Stable	107 (61.8%)	68 (78.2%)
Deteriorated	9 (5.2%)	6 (6.9%)
p-value	0.0026	

PVR= pulmonary vascular resistance

NT-proBNP =N-terminal prohormone of brain natriuretic peptide

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat IDT 1.0-2.5 mg, 2.9%; placebo, 2.3%).

Long-term treatment

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily.
The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group.

The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.

Efficacy in patients with PAH

A randomised, double-blind, multi-national, placebo controlled, phase III study (PATENT-1) was conducted in 443 adult patients with PAH (riociguat individual dose titration up to 2.5 mg three times daily: n=254, placebo: n=126, riociguat “capped” dose titration (CT) up to 1.5 mg (exploratory dose arm, no statistical testing performed; n=63)). Patients were either treatment-naïve (50%) or pre-treated with an endothelin receptor antagonist (ERA; 43%) or a prostacyclin analogue (inhaled (iloprost), oral (beraprost) or subcutaneous (treprostinil); 7%) and had been diagnosed with idiopathic or heritable PAH (63.4%), PAH associated with connective tissue disease (25.1%) and congenital heart disease (7.9%).
During the first 8 weeks riociguat was titrated every 2-weeks based on the patient’s systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg

three times daily), which was then maintained for a further 4 weeks. The primary endpoint of the study was placebo-adjusted change from baseline in 6MWD at the last visit (week 12).

At the last visit the increase in 6MWD with riociguat individual dose titration (IDT) was 36 m (95% CI: 20 m to 52 m; p<0.0001) compared to placebo. Treatment-naïve patients (n=189) improved by 38 m, and pre-treated patients (n=191) by 36 m (ITT analysis, see table 4). Further exploratory subgroup analysis revealed a treatment effect of 26 m, (95% CI: 5 m to 46 m) in patients pre-treated with ERAs (n=167) and a treatment effect of 101 m (95% CI: 27 m to 176 m) in patients pre-treated with prostacyclin analogues (n=27).

Table 4: Effects of riociguat on 6MWD in PATENT-1 at last visit

Entire patient population	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Baseline (m) [SD]	361 [68]	368 [75]	363 [67]
Mean change from baseline (m) [SD]	30 [66]	-6 [86]	31 [79]
Placebo-adjusted difference (m) 95% CI, [p-value]	36 20 to 52 [<0.0001]		
FC III patients	**Riociguat IDT (n=140)**	**Placebo (n=58)**	**Riociguat CT (n=39)**
Baseline (m) [SD]	338 [70]	347 [78]	351 [68]
Mean change from baseline (m) [SD]	31 [64]	-27 [98]	29 [94]
Placebo-adjusted difference (m) 95% CI	58 35 to 81		
FC II patients	**Riociguat IDT (n=108)**	**Placebo (n=60)**	**Riociguat CT (n=19)**
Baseline (m) [SD]	392 [51]	393 [61]	378 [64]
Mean change from baseline (m) [SD]	29 [69]	19 [63]	43 [50]
Placebo-adjusted difference (m) 95% CI	10 -11 to 31		
Treatment-naïve patient population	**Riociguat IDT (n=123)**	**Placebo (n=66)**	**Riociguat CT (n=32)**
Baseline (m) [SD]	370 [66]	360 [80]	347 [72]
Mean change from baseline (m) [SD]	32 [74]	-6 [88]	49 [47]
Placebo-adjusted difference (m) 95% CI	38 14 to 62		
Pre-treated patient population	**Riociguat IDT (n=131)**	**Placebo (n=60)**	**Riociguat CT (n=31)**
Baseline (m) [SD]	353 [69]	376 [68]	380 [57]
Mean change from baseline (m) [SD]	27 [58]	-5 [83]	12 [100]
Placebo- adjusted difference (m) 95% CI	36 15 to 56		

Improvement in exercise capacity was accompanied by consistent improvement in multiple clinically-relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters (see table 5).

Table 5: Effects of riociguat in PATENT-1 on PVR and NT-proBNP at last visit

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm-5) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	1026.7 [1799.2]	1228.1 [1774.9]	1189.7 [1404.7]
Mean change from baseline (ng/L) [SD]	-197.9 [1721.3]	232.4 [1011.1]	-471.5 [913.0]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-431.8 (-781.5 to -82.1) [<0.0001]		
Change in WHO Functional Class	**Riociguat IDT (n = 254)**	**Placebo (n = 125)**	**Riociguat CT (n=63)**
Improved	53 (20.9%)	18 (14.4%)	15 (23.8%)
Stable	192 (75.6%)	89 (71.2%)	43 (68.3%)
Deteriorated	9 (3.6%)	18 (14.4%)	5 (7.9%)
p-value	0.0033		

Riociguat-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test) (see table 6).

Table 6: Effects of riociguat in PATENT-1 on events of clinical worsening

Clinical Worsening Events	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Patients with any clinical worsening	3 (1.2%)	8 (6.3%)	2 (3.2%)
Death	2 (0.8%)	3 (2.4%)	1 (1.6%)
Hospitalisations due to PH	1 (0.4%)	4 (3.2%)	0
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)	1 (1.6%)
Persistent worsening of Functional Class due to PH	0	1 (0.8%)	0
Start of new PH treatment	1 (0.4%)	5 (4.0%)	1 (1.6%)

Patients treated with riociguat showed significant improvement in Borg CR 10 dyspnoea score (mean change from baseline (SD): riociguat -0.4 (2), placebo 0.1 (2); p = 0.0022).

Adverse Events leading to discontinuation occurred less frequently in both riociguat treatment groups than in the placebo group (riociguat IDT 1.0-2.5 mg, 3.1%; riociguat CT 1.6%; placebo, 7.1%).

Long-term treatment

An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.

The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adempas in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.
See section 4.2 for information on paediatric use.

5.2 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 reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-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 M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.
CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found 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 12 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%.

Special populations

Gender
Pharmacokinetic data reveal no relevant differences due to gender in the exposure to riociguat.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients.

Elderly population
Elderly patients (65 years or older) 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.

Inter-ethnic differences
Pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
Pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

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. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).

Patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied (see section 4.4).

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 (creatinine clearance 80-50 mL/min), moderate (creatinine clearance <50-30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively.
Data in patients with creatinine clearance <30 mL/min are limited and there are no data for patients on dialysis.
Due to the high plasma protein binding riociguat is not expected to be dialysable.

5.3 Preclinical safety data

Non-clinical data revealed no specific hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity and carcinogenicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of riociguat (haemodynamic and smooth muscle relaxing effects).

In growing, juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats.

In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. Moderate passage across the placental barrier was observed. 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-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cellulose microcrystalline
crospovidone
hypromellose
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose
propylene glycol
titanium dioxide (E 171)
ferric oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.
Pack sizes: 42, 84 or 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/007
EU/1/13/907/008
EU/1/13/907/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Adempas 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg of riociguat.

Excipients with known effect:

Each film-coated tablet contains 36.3 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2 and an "R" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

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

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2).

Dose should be increased by 0.5 mg three times daily every two weeks 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. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1). If systolic blood pressure falls below 95 mmHg, the dose 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 current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (see section 5.2).

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 adjustment of the dose to the patient´s needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone (see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is contraindicated in these patients (see section 4.3). Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients (see section 4.4).

Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2).
A dose decrease may be required in patients who stop smoking.

Method of administration

For oral use.

4.3 Contraindications

- Co-administration with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see section 4.5)
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see section 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).
In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.
The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.
Serious bleeding occurred in 2.4% (12 /490) of patients taking riociguat compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking riociguat compared to 0/214 patients taking placebo, 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.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).
Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients (see section 5.2). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients (see section 4.3). PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B) (see section 5.2). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat (see sections 4.2 and 5.2).

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see section 4.5 and 5.2).
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see section 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone

(see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

Information about excipients

Each 2 mg film coated tablet contains 36.3 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see section 4.3).

PDE 5 inhibitors
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 an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) 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 to 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part of this study (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 use of riociguat with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.3).

Warfarin/phenprocoumon
Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other cumarin-derivatives (e.g. phenprocoumon) is also not expected to alter prothrombin time.
Lack of pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetylsalicylic acid
Riociguat did not potentiate the bleeding time caused by acetyl-salicylic acid or affect the platelet aggregation in humans.

Effects of other substances on riociguat

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

In vitro, ketoconazole, classified as a 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 (see section 5.2). 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.

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 section 4.4).

Drugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive cyclosporine A, should be used with caution (see sections 4.4 and 5.2).

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: $1/10^{th}$ to $1/3^{rd}$ of riociguat).

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 catalysed formation of riociguat's main metabolite most effectively. 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 (see section 5.2). Strong CYP1A1 inhibitors should be used with caution (see section 4.4).

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.

Co-administration of the antacid aluminium hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see section 4.2). Antacids should be taken at least 2 hours before, or 1 hour after riociguat.

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1).

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

Smoking
In cigarette smokers riociguat exposure is reduced by 50-60% (see section 5.2). Therefore, patients are advised to stop smoking (see section 4.2).

Effects of riociguat on other substances

Riociguat and its main metabolite are not inhibitors or inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations.
Riociguat and its main metabolite are 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer (see section 5.3). Therefore, Adempas is contraindicated during pregnancy (see section 4.3). Monthly pregnancy tests are recommended.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Adempas.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with this medicine.

Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, decreased testes weights were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicine, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1).

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

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

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see section 4.4).

The safety profile of Adempas in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with Adempas are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with Adempas in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Epistaxis Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhoea Nausea Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,
ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system 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 is associated with endothelial dysfunction, impaired synthesis of NO 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 independently of NO.
Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.
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 efficacy and safety

Efficacy in patients with CTEPH

A randomised, double-blind, multi-national, placebo controlled, phase III study (CHEST-1) was conducted in 261 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (72%) or persistent or recurrent CTEPH after pulmonary endarterectomy (PEA; 28%). During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily) which was then maintained for a further 8 weeks. The primary endpoint of the study was the placebo adjusted change from baseline in 6-minute walk distance (6MWD) at the last visit (week 16).
At the last visit, the increase in 6MWD in patients treated with riociguat was 46 m (95% confidence interval (CI): 25 m to 67 m; $p<0.0001$), compared to placebo. Results were consistent in the main sub-groups evaluated (ITT analysis, see table 2).

Table 2: Effects of riociguat on 6MWD in CHEST-1 at last visit

Entire patient population	**Riociguat (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Mean change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-adjusted difference (m) 95% CI, [p-value]	46 25 to 67 [<0.0001]	
FC III patient population	**Riociguat (n=107)**	**Placebo (n=60)**
Baseline (m) [SD]	326 [81]	345 [73]
Mean change from baseline (m) [SD]	38 [75]	-17 [95]
Placebo-adjusted difference (m) 95% CI	56 29 to 83	
FC II patient population	**Riociguat (n=55)**	**Placebo (n=25)**
Baseline (m) [SD]	387 [59]	386 [64]
Mean change from baseline (m) [SD]	45 [82]	20 [51]
Placebo-adjusted difference (m) 95% CI	25 -10 to 61	
Inoperable patient population	**Riociguat (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Mean change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-adjusted difference (m) 95% CI	54 29 to 79	
Patient population with CTEPH post-PEA	**Riociguat (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Mean change from baseline (m) [SD]	27 [68]	1.8 [73]
Placebo- adjusted mean LS-difference (m) 95% CI	27 -10 to 63	

LS=least squares

Improvement in exercise capacity was accompanied by improvement in multiple clinically relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters.

Table 3: Effects of riociguat in CHEST-1 on PVR, NT-proBNP and WHO functional class at last visit

PVR	**Riociguat (n=151)**	**Placebo (n=82)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-246.4 –303.3 to –189.5 [<0.0001]	
NT-proBNP	**Riociguat (n=150)**	**Placebo (n=73)**
Baseline (ng/L) [SD]	1508.3 [2337.8]	1705.8 [2567.2]
Mean change from baseline (ng/L) [SD]	-290.7 [1716.9]	76.4 [1446.6]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-444.0 -843.0 to -45.0 [<0.0001]	
Change in WHO Functional Class	**Riociguat (n=173)**	**Placebo (n=87)**
Improved	57 (32.9%)	13 (14.9%)
Stable	107 (61.8%)	68 (78.2%)
Deteriorated	9 (5.2%)	6 (6.9%)
p-value	0.0026	

PVR= pulmonary vascular resistance

NT-proBNP =N-terminal prohormone of brain natriuretic peptide

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat IDT 1.0-2.5 mg, 2.9%; placebo, 2.3%).

Long-term treatment

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group.

The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.

Efficacy in patients with PAH

A randomised, double-blind, multi-national, placebo controlled, phase III study (PATENT-1) was conducted in 443 adult patients with PAH (riociguat individual dose titration up to 2.5 mg three times daily: n=254, placebo: n=126, riociguat “capped” dose titration (CT) up to 1.5 mg (exploratory dose arm, no statistical testing performed; n=63)). Patients were either treatment-naïve (50%) or pre-treated with an endothelin receptor antagonist (ERA; 43%) or a prostacyclin analogue (inhaled (iloprost), oral (beraprost) or subcutaneous (treprostinil); 7%) and had been diagnosed with idiopathic or heritable PAH (63.4%), PAH associated with connective tissue disease (25.1%) and congenital heart disease (7.9%).

During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily), which was then maintained for a further 4 weeks. The primary endpoint of the study was placebo-adjusted change from baseline in 6MWD at the last visit (week 12).

At the last visit the increase in 6MWD with riociguat individual dose titration (IDT) was 36 m (95% CI: 20 m to 52 m; $p<0.0001$) compared to placebo. Treatment-naïve patients (n=189) improved by 38 m, and pre-treated patients (n=191) by 36 m (ITT analysis, see table 4). Further exploratory subgroup analysis revealed a treatment effect of 26 m, (95% CI: 5 m to 46 m) in patients pre-treated with ERAs (n=167) and a treatment effect of 101 m (95% CI: 27 m to 176 m) in patients pre-treated with prostacyclin analogues (n=27).

Table 4: Effects of riociguat on 6MWD in PATENT-1 at last visit

Entire patient population	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Baseline (m) [SD]	361 [68]	368 [75]	363 [67]
Mean change from baseline (m) [SD]	30 [66]	-6 [86]	31 [79]
Placebo-adjusted difference (m) 95% CI, [p-value]	36 20 to 52 [<0.0001]		
FC III patients	**Riociguat IDT (n=140)**	**Placebo (n=58)**	**Riociguat CT (n=39)**
Baseline (m) [SD]	338 [70]	347 [78]	351 [68]
Mean change from baseline (m) [SD]	31 [64]	-27 [98]	29 [94]
Placebo-adjusted difference (m) 95% CI	58 35 to 81		
FC II patients	**Riociguat IDT (n=108)**	**Placebo (n=60)**	**Riociguat CT (n=19)**
Baseline (m) [SD]	392 [51]	393 [61]	378 [64]
Mean change from baseline (m) [SD]	29 [69]	19 [63]	43 [50]
Placebo-adjusted difference (m) 95% CI	10 -11 to 31		
Treatment-naïve patient population	**Riociguat IDT (n=123)**	**Placebo (n=66)**	**Riociguat CT (n=32)**
Baseline (m) [SD]	370 [66]	360 [80]	347 [72]
Mean change from baseline (m) [SD]	32 [74]	-6 [88]	49 [47]
Placebo-adjusted difference (m) 95% CI	38 14 to 62		
Pre-treated patient population	**Riociguat IDT (n=131)**	**Placebo (n=60)**	**Riociguat CT (n=31)**
Baseline (m) [SD]	353 [69]	376 [68]	380 [57]
Mean change from baseline (m) [SD]	27 [58]	-5 [83]	12 [100]
Placebo- adjusted difference (m) 95% CI	36 15 to 56		

Improvement in exercise capacity was accompanied by consistent improvement in multiple clinically-relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters (see table 5).

Table 5: Effects of riociguat in PATENT-1 on PVR and NT-proBNP at last visit

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm-5) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	1026.7 [1799.2]	1228.1 [1774.9]	1189.7 [1404.7]
Mean change from baseline (ng/L) [SD]	-197.9 [1721.3]	232.4 [1011.1]	-471.5 [913.0]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-431.8 (-781.5 to -82.1) [<0.0001]		
Change in WHO Functional Class	**Riociguat IDT (n = 254)**	**Placebo (n = 125)**	**Riociguat CT (n=63)**
Improved	53 (20.9%)	18 (14.4%)	15 (23.8%)
Stable	192 (75.6%)	89 (71.2%)	43 (68.3%)
Deteriorated	9 (3.6%)	18 (14.4%)	5 (7.9%)
p-value	0.0033		

Riociguat-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test) (see table 6).

Table 6: Effects of riociguat in PATENT-1 on events of clinical worsening

Clinical Worsening Events	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Patients with any clinical worsening	3 (1.2%)	8 (6.3%)	2 (3.2%)
Death	2 (0.8%)	3 (2.4%)	1 (1.6%)
Hospitalisations due to PH	1 (0.4%)	4 (3.2%)	0
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)	1 (1.6%)
Persistent worsening of Functional Class due to PH	0	1 (0.8%)	0
Start of new PH treatment	1 (0.4%)	5 (4.0%)	1 (1.6%)

Patients treated with riociguat showed significant improvement in Borg CR 10 dyspnoea score (mean change from baseline (SD): riociguat -0.4 (2), placebo 0.1 (2); p = 0.0022).

Adverse Events leading to discontinuation occurred less frequently in both riociguat treatment groups than in the placebo group (riociguat IDT 1.0-2.5 mg, 3.1%; riociguat CT 1.6%; placebo, 7.1%).

Long-term treatment

An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.

The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adempas in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.
See section 4.2 for information on paediatric use.

5.2 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 reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-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 M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.
CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found 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 12 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%.

Special populations

Gender
Pharmacokinetic data reveal no relevant differences due to gender in the exposure to riociguat.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients.

Elderly population
Elderly patients (65 years or older) 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.

Inter-ethnic differences
Pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
Pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

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. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).

Patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied (see section 4.4).

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 (creatinine clearance 80-50 mL/min), moderate (creatinine clearance <50-30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively.
Data in patients with creatinine clearance <30 mL/min are limited and there are no data for patients on dialysis.
Due to the high plasma protein binding riociguat is not expected to be dialysable.

5.3 Preclinical safety data

Non-clinical data revealed no specific hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity and carcinogenicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of riociguat (haemodynamic and smooth muscle relaxing effects).

In growing, juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats.

In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. Moderate passage across the placental barrier was observed. 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-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cellulose microcrystalline
crospovidone
hypromellose
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose
propylene glycol
titanium dioxide (E 171)
ferric oxide red (E 172)
ferric oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.
Pack sizes: 42, 84 or 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/010
EU/1/13/907/011
EU/1/13/907/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Adempas 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg of riociguat.

Excipients with known effect:

Each film-coated tablet contains 35.8 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Red-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2.5 and an "R" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity (see section 5.1).

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

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

Posology

Dose titration
The recommended starting dose is 1 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart (see section 5.2).

Dose should be increased by 0.5 mg three times daily every two weeks 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. In some PAH patients, an adequate response on the 6-minute walk distance (6MWD) may be reached at a dose of 1.5 mg three times a day (see section 5.1). If systolic blood pressure falls below 95 mmHg, the dose 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 current dose should be decreased by 0.5 mg three times daily.

Maintenance dose
The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned.
If not tolerated, dose reduction should be considered at any time.

Food
Tablets can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted Adempas intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (see section 5.2).

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 adjustment of the dose to the patient´s needs.

Paediatric population
The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone (see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided (see section 4.4).

Elderly population
In elderly patients (65 years or older) there is a higher risk of hypotension and therefore particular care should be exercised during individual dose titration (see section 5.2).

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is contraindicated in these patients (see section 4.3). Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to this medicine (see section 5.2). Particular care should be exercised during individual dose titration.

Renal impairment
Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore use of Adempas is not recommended in these patients (see section 4.4).

Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Smokers
Current smokers should be advised to stop smoking due to a risk of a lower response. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. A dose increase to the maximum daily dose of 2.5 mg three times daily may be required in patients who are smoking or start smoking during treatment (see section 4.5 and 5.2).
A dose decrease may be required in patients who stop smoking.

Method of administration

For oral use.

4.3 Contraindications

- Co-administration with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see section 4.5)
- Severe hepatic impairment (Child Pugh C).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see section 4.5).
- Patients with systolic blood pressure < 95 mm Hg at treatment initiation.

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).
In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of riociguat to such patients is not recommended. Should signs of pulmonary oedema occur, the possibility of associated PVOD should be considered and treatment with riociguat should be discontinued.

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.
The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.
Serious bleeding occurred in 2.4% (12 /490) of patients taking riociguat compared to 0/214 of placebo patients. Serious haemoptysis occurred in 1% (5/490) patients taking riociguat compared to 0/214 patients taking placebo, 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.

Hypotension

Riociguat has vasodilatory properties which may result in lowering of blood pressure. Before prescribing riociguat, physicians should carefully consider whether patients with certain underlying conditions, could be adversely affected by vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolaemia, severe left ventricular outflow obstruction or autonomic dysfunction).
Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

Data in patients with severe renal impairment (creatinine clearance < 30 mL/min) are limited and there are no data for patients on dialysis, therefore riociguat is not recommended in these patients. Patients with mild and moderate renal impairment were included in the pivotal studies. There is increased riociguat exposure in these patients (see section 5.2). There is a higher risk of hypotension in these patients, particular care should be exercised during individual dose titration.

Hepatic impairment

There is no experience in patients with severe hepatic impairment (Child Pugh C); riociguat is contraindicated in these patients (see section 4.3). PK data show that higher riociguat exposure was observed in patients with moderate hepatic impairment (Child Pugh B) (see section 5.2). Particular care should be exercised during individual dose titration.

There is no clinical experience with riociguat in patients with elevated liver aminotransferases (> 3 x Upper Limit of Normal (ULN)) or with elevated direct bilirubin (> 2 x ULN) prior to initiation of treatment; riociguat is not recommended in these patients.

Smokers

Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment may be necessary in patients who start or stop smoking during treatment with riociguat (see sections 4.2 and 5.2).

Concomitant use with other medicinal products

- The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the pronounced increase in riociguat exposure (see section 4.5 and 5.2).
- The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure (see section 4.5 and 5.2). These medicinal products should be used with caution. Blood pressure should be monitored and dose reduction of riociguat be considered.

Paediatric population

The safety and efficacy of riociguat in children and adolescents below 18 years have not been established. No clinical data are available. Non-clinical data show an adverse effect on growing bone

(see section 5.3). Until more is known about the implications of these findings the use of riociguat in children and in growing adolescents should be avoided.

Information about excipients

Each 2.5 mg film coated tablet contains 35.8 mg lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see section 4.3).

PDE 5 inhibitors
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 an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) 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 to 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part of this study (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 use of riociguat with PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see section 4.3).

Warfarin/phenprocoumon
Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other cumarin-derivatives (e.g. phenprocoumon) is also not expected to alter prothrombin time.
Lack of pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetylsalicylic acid
Riociguat did not potentiate the bleeding time caused by acetyl-salicylic acid or affect the platelet aggregation in humans.

Effects of other substances on riociguat

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

In vitro, ketoconazole, classified as a 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 (see section 5.2). 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.

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 section 4.4).

Drugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive cyclosporine A, should be used with caution (see sections 4.4 and 5.2).

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: $1/10^{th}$ to $1/3^{rd}$ of riociguat).

From the recombinant CYP isoforms investigated *in vitro* CYP1A1 catalysed formation of riociguat's main metabolite most effectively. 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 (see section 5.2). Strong CYP1A1 inhibitors should be used with caution (see section 4.4).

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.

Co-administration of the antacid aluminium hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% (see section 4.2). Antacids should be taken at least 2 hours before, or 1 hour after riociguat.

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1).

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

Smoking
In cigarette smokers riociguat exposure is reduced by 50-60% (see section 5.2). Therefore, patients are advised to stop smoking (see section 4.2).

Effects of riociguat on other substances

Riociguat and its main metabolite are not inhibitors or inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations. Riociguat and its main metabolite are 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and placental transfer (see section 5.3). Therefore, Adempas is contraindicated during pregnancy (see section 4.3). Monthly pregnancy tests are recommended.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Adempas.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with this medicine.

Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, decreased testes weights were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicine, before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1).

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

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

Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas (see section 4.4).

The safety profile of Adempas in patients with CTEPH and PAH appeared to be similar, therefore adverse reactions identified from placebo controlled 12 and 16 weeks clinical studies are presented as pooled frequency in the table listed below (see table 1).

Tabulated list of adverse reactions

The adverse reactions reported with Adempas are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 1: Adverse reactions reported with Adempas in the phase III studies

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anaemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Haemoptysis Epistaxis Nasal congestion	Pulmonary haemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhoea Nausea Vomiting	Gastritis, Gastro-oesophageal reflux disease, Dysphagia, Gastrointestinal and abdominal pains, Constipation, Abdominal distension	
General disorders and administration site conditions	Oedema peripheral		

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Inadvertent overdosing with total daily doses of 9 to 25 mg riociguat between 2 to 32 days was reported. Adverse reactions were similar to those seen at lower doses (see section 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,
ATC code: C02KX05

Mechanism of action

Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system 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 is associated with endothelial dysfunction, impaired synthesis of NO 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 independently of NO.
Riociguat restores the NO-sGC-cGMP pathway and leads to increased generation of cGMP.

Pharmacodynamic effects

Riociguat restores the NO-sGC-cGMP pathway resulting in a significant improvement of pulmonary vascular haemodynamics and an increase in exercise ability.
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 efficacy and safety

Efficacy in patients with CTEPH

A randomised, double-blind, multi-national, placebo controlled, phase III study (CHEST-1) was conducted in 261 adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (72%) or persistent or recurrent CTEPH after pulmonary endarterectomy (PEA; 28%). During the first 8 weeks riociguat was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg three times daily) which was then maintained for a further 8 weeks. The primary endpoint of the study was the placebo adjusted change from baseline in 6-minute walk distance (6MWD) at the last visit (week 16).
At the last visit, the increase in 6MWD in patients treated with riociguat was 46 m (95% confidence interval (CI): 25 m to 67 m; $p<0.0001$), compared to placebo. Results were consistent in the main sub-groups evaluated (ITT analysis, see table 2).

Table 2: Effects of riociguat on 6MWD in CHEST-1 at last visit

Entire patient population	**Riociguat (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Mean change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-adjusted difference (m) 95% CI, [p-value]	46 25 to 67 [<0.0001]	
FC III patient population	**Riociguat (n=107)**	**Placebo (n=60)**
Baseline (m) [SD]	326 [81]	345 [73]
Mean change from baseline (m) [SD]	38 [75]	-17 [95]
Placebo-adjusted difference (m) 95% CI	56 29 to 83	
FC II patient population	**Riociguat (n=55)**	**Placebo (n=25)**
Baseline (m) [SD]	387 [59]	386 [64]
Mean change from baseline (m) [SD]	45 [82]	20 [51]
Placebo-adjusted difference (m) 95% CI	25 -10 to 61	
Inoperable patient population	**Riociguat (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Mean change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-adjusted difference (m) 95% CI	54 29 to 79	
Patient population with CTEPH post-PEA	**Riociguat (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Mean change from baseline (m) [SD]	27 [68]	1.8 [73]
Placebo- adjusted mean LS-difference (m) 95% CI	27 -10 to 63	

LS=least squares

Improvement in exercise capacity was accompanied by improvement in multiple clinically relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters.

Table 3: Effects of riociguat in CHEST-1 on PVR, NT-proBNP and WHO functional class at last visit

PVR	**Riociguat (n=151)**	**Placebo (n=82)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-246.4 –303.3 to –189.5 [<0.0001]	
NT-proBNP	**Riociguat (n=150)**	**Placebo (n=73)**
Baseline (ng/L) [SD]	1508.3 [2337.8]	1705.8 [2567.2]
Mean change from baseline (ng/L) [SD]	-290.7 [1716.9]	76.4 [1446.6]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-444.0 -843.0 to -45.0 [<0.0001]	
Change in WHO Functional Class	**Riociguat (n=173)**	**Placebo (n=87)**
Improved	57 (32.9%)	13 (14.9%)
Stable	107 (61.8%)	68 (78.2%)
Deteriorated	9 (5.2%)	6 (6.9%)
p-value	0.0026	

PVR= pulmonary vascular resistance

NT-proBNP =N-terminal prohormone of brain natriuretic peptide

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat IDT 1.0-2.5 mg, 2.9%; placebo, 2.3%).

Long-term treatment

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group.

The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.

Efficacy in patients with PAH

A randomised, double-blind, multi-national, placebo controlled, phase III study (PATENT-1) was conducted in 443 adult patients with PAH (riociguat individual dose titration up to 2.5 mg three times daily: n=254, placebo: n=126, riociguat “capped” dose titration (CT) up to 1.5 mg (exploratory dose arm, no statistical testing performed; n=63)). Patients were either treatment-naïve (50%) or pre-treated with an endothelin receptor antagonist (ERA; 43%) or a prostacyclin analogue (inhaled (iloprost), oral (beraprost) or subcutaneous (treprostinil); 7%) and had been diagnosed with idiopathic or heritable PAH (63.4%), PAH associated with connective tissue disease (25.1%) and congenital heart disease (7.9%).

During the first 8 weeks riociguat was titrated every 2-weeks based on the patient’s systolic blood pressure and signs or symptoms of hypotension to the optimal individual dose (range 0.5 mg to 2.5 mg

three times daily), which was then maintained for a further 4 weeks. The primary endpoint of the study was placebo-adjusted change from baseline in 6MWD at the last visit (week 12).

At the last visit the increase in 6MWD with riociguat individual dose titration (IDT) was 36 m (95% CI: 20 m to 52 m; $p<0.0001$) compared to placebo. Treatment-naïve patients (n=189) improved by 38 m, and pre-treated patients (n=191) by 36 m (ITT analysis, see table 4). Further exploratory subgroup analysis revealed a treatment effect of 26 m, (95% CI: 5 m to 46 m) in patients pre-treated with ERAs (n=167) and a treatment effect of 101 m (95% CI: 27 m to 176 m) in patients pre-treated with prostacyclin analogues (n=27).

Table 4: Effects of riociguat on 6MWD in PATENT-1 at last visit

Entire patient population	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Baseline (m) [SD]	361 [68]	368 [75]	363 [67]
Mean change from baseline (m) [SD]	30 [66]	-6 [86]	31 [79]
Placebo-adjusted difference (m) 95% CI, [p-value]	36 20 to 52 [<0.0001]		
FC III patients	**Riociguat IDT (n=140)**	**Placebo (n=58)**	**Riociguat CT (n=39)**
Baseline (m) [SD]	338 [70]	347 [78]	351 [68]
Mean change from baseline (m) [SD]	31 [64]	-27 [98]	29 [94]
Placebo-adjusted difference (m) 95% CI	58 35 to 81		
FC II patients	**Riociguat IDT (n=108)**	**Placebo (n=60)**	**Riociguat CT (n=19)**
Baseline (m) [SD]	392 [51]	393 [61]	378 [64]
Mean change from baseline (m) [SD]	29 [69]	19 [63]	43 [50]
Placebo-adjusted difference (m) 95% CI	10 -11 to 31		
Treatment-naïve patient population	**Riociguat IDT (n=123)**	**Placebo (n=66)**	**Riociguat CT (n=32)**
Baseline (m) [SD]	370 [66]	360 [80]	347 [72]
Mean change from baseline (m) [SD]	32 [74]	-6 [88]	49 [47]
Placebo-adjusted difference (m) 95% CI	38 14 to 62		
Pre-treated patient population	**Riociguat IDT (n=131)**	**Placebo (n=60)**	**Riociguat CT (n=31)**
Baseline (m) [SD]	353 [69]	376 [68]	380 [57]
Mean change from baseline (m) [SD]	27 [58]	-5 [83]	12 [100]
Placebo- adjusted difference (m) 95% CI	36 15 to 56		

Improvement in exercise capacity was accompanied by consistent improvement in multiple clinically-relevant secondary endpoints. These findings were in accordance with improvements in additional haemodynamic parameters (see table 5).

Table 5: Effects of riociguat in PATENT-1 on PVR and NT-proBNP at last visit

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm-5) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	1026.7 [1799.2]	1228.1 [1774.9]	1189.7 [1404.7]
Mean change from baseline (ng/L) [SD]	-197.9 [1721.3]	232.4 [1011.1]	-471.5 [913.0]
Placebo-adjusted difference (ng/L) 95% CI, [p-value]	-431.8 (-781.5 to -82.1) [<0.0001]		
Change in WHO Functional Class	**Riociguat IDT (n = 254)**	**Placebo (n = 125)**	**Riociguat CT (n=63)**
Improved	53 (20.9%)	18 (14.4%)	15 (23.8%)
Stable	192 (75.6%)	89 (71.2%)	43 (68.3%)
Deteriorated	9 (3.6%)	18 (14.4%)	5 (7.9%)
p-value	0.0033		

Riociguat-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test) (see table 6).

Table 6: Effects of riociguat in PATENT-1 on events of clinical worsening

Clinical Worsening Events	**Riociguat IDT (n=254)**	**Placebo (n=126)**	**Riociguat CT (n=63)**
Patients with any clinical worsening	3 (1.2%)	8 (6.3%)	2 (3.2%)
Death	2 (0.8%)	3 (2.4%)	1 (1.6%)
Hospitalisations due to PH	1 (0.4%)	4 (3.2%)	0
Decrease in 6MWD due to PH	1 (0.4%)	2 (1.6%)	1 (1.6%)
Persistent worsening of Functional Class due to PH	0	1 (0.8%)	0
Start of new PH treatment	1 (0.4%)	5 (4.0%)	1 (1.6%)

Patients treated with riociguat showed significant improvement in Borg CR 10 dyspnoea score (mean change from baseline (SD): riociguat -0.4 (2), placebo 0.1 (2); p = 0.0022).

Adverse Events leading to discontinuation occurred less frequently in both riociguat treatment groups than in the placebo group (riociguat IDT 1.0-2.5 mg, 3.1%; riociguat CT 1.6%; placebo, 7.1%).

Long-term treatment

An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.

The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Adempas in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.
See section 4.2 for information on paediatric use.

5.2 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 reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and alpha 1-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 M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.
CYP1A1 catalyses the formation of riociguat's main metabolite in liver and lungs and is known to be inducible by polycyclic aromatic hydrocarbons, which, for example, are present in cigarette smoke.

Elimination

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/faecal routes (48-59%). Approximately 4-19% of the administered dose was excreted as unchanged riociguat via the kidneys. Approximately 9-44% of the administered dose was found 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 12 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%.

Special populations

Gender
Pharmacokinetic data reveal no relevant differences due to gender in the exposure to riociguat.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of riociguat in paediatric patients.

Elderly population
Elderly patients (65 years or older) 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.

Inter-ethnic differences
Pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
Pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

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. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).

Patients with ALT > 3 x ULN and bilirubin > 2 x ULN were not studied (see section 4.4).

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 (creatinine clearance 80-50 mL/min), moderate (creatinine clearance <50-30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 53%, 139% or 54%, respectively.
Data in patients with creatinine clearance <30 mL/min are limited and there are no data for patients on dialysis.
Due to the high plasma protein binding riociguat is not expected to be dialysable.

5.3 Preclinical safety data

Non-clinical data revealed no specific hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity and carcinogenicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of riociguat (haemodynamic and smooth muscle relaxing effects).

In growing, juvenile and adolescent rats, effects on bone formation were seen. In juvenile rats, the changes consisted of thickening of trabecular bone and of hyperostosis and remodeling of metaphyseal and diaphyseal bone, whereas in adolescent rats an overall increase of bone mass was observed. No such effects were observed in adult rats.

In a fertility study in rats, decreased testes weights occurred at systemic exposure of about 7-fold of human exposure, whereas no effects on male and female fertility were seen. Moderate passage across the placental barrier was observed. 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-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of about 3-fold of human exposure (2.5 mg three times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

cellulose microcrystalline
crospovidone
hypromellose
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose
propylene glycol
titanium dioxide (E 171)
ferric oxide red (E 172)
ferric oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.
Pack sizes: 42, 84 or 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/013
EU/1/13/907/014
EU/1/13/907/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Bayer Pharma AG
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.5 mg film-coated tablets
Adempas 1 mg film-coated tablets
Adempas 1.5 mg film-coated tablets
Adempas 2 mg film-coated tablets
Adempas 2.5 mg film-coated tablets
riociguat

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 0.5 mg, 1 mg, 1.5 mg, 2 mg or 2.5 mg riociguat.

3. LIST OF EXCIPIENTS

Contains lactose. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

42 film-coated tablets
84 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

Bayer (logo)

12. MARKETING AUTHORISATION NUMBER

Adempas 0.5 mg – pack of 42 film-coated tablets - EU/1/13/907/001
Adempas 0.5 mg – pack of 84 film-coated tablets - EU/1/13/907/002
Adempas 0.5 mg – pack of 90 film-coated tablets - EU/1/13/907/003
Adempas 1 mg – pack of 42 film-coated tablets - EU/1/13/907/004
Adempas 1 mg – pack of 84 film-coated tablets - EU/1/13/907/005
Adempas 1 mg – pack of 90 film-coated tablets - EU/1/13/907/006
Adempas 1.5 mg – pack of 42 film-coated tablets - EU/1/13/907/007
Adempas 1.5 mg – pack of 84 film-coated tablets - EU/1/13/907/008
Adempas 1.5 mg – pack of 90 film-coated tablets - EU/1/13/907/009
Adempas 2 mg – pack of 42 film-coated tablets - EU/1/13/907/010
Adempas 2 mg – pack of 84 film-coated tablets - EU/1/13/907/011
Adempas 2 mg – pack of 90 film-coated tablets - EU/1/13/907/012
Adempas 2.5 mg – pack of 42 film-coated tablets - EU/1/13/907/013
Adempas 2.5 mg – pack of 84 film-coated tablets - EU/1/13/907/014
Adempas 2.5 mg – pack of 90 film-coated tablets - EU/1/13/907/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Adempas 0.5 mg, 1 mg, 1.5 mg, 2 mg or 2.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - PACKS OF 42, 84; 90 FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.5 mg film-coated tablets
Adempas 1 mg film-coated tablets
Adempas 1.5 mg film-coated tablets
Adempas 2 mg film-coated tablets
Adempas 2.5 mg film-coated tablets
riociguat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

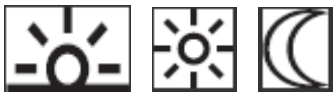
EXP

4. BATCH NUMBER

Lot

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN



B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Adempas 0.5 mg film-coated tablets
Adempas 1 mg film-coated tablets
Adempas 1.5 mg film-coated tablets
Adempas 2 mg film-coated tablets
Adempas 2.5 mg film-coated tablets

Riociguat

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Adempas is and what it is used for

Adempas contains the active substance riociguat. Riociguat is a type of medicine called a guanylate cyclase (sGC)-stimulator.It works by widening the pulmonary arteries (the blood vessels that connect the heart to the lungs), making it easier for the heart to pump blood through the lungs. Adempas can be used to treat adults with certain forms of pulmonary hypertension, a condition in which these blood vessels become narrowed, making it harder for the heart to pump blood through them and leading to high blood pressure in the vessels. Because the heart must work harder than normal, people with pulmonary hypertension feel tired, dizzy and short of breath. By widening the narrowed arteries, Adempas leads to an improvement in your ability to carry out physical activity.

Adempas is used in either of two types of pulmonary hypertension:

- **chronic thromboembolic pulmonary hypertension (CTEPH)**.
  In CTEPH, the blood vessels of the lung are blocked or narrowed with blood clots. Adempas can be used for patients with CTEPH who cannot be operated on, or after surgery for patients in whom increased blood pressure in the lungs remains or returns.
- **certain types of pulmonary arterial hypertension (PAH)**.
  In PAH, the wall of the blood vessels of the lungs are thickened and the vessels become narrowed. Adempas is only prescribed for certain forms of PAH, i.e. idiopathic PAH (the cause of PAH is unknown), heritable PAH and PAH caused by connective tissue disease. Your doctor

will check this. Adempas can be taken alone or together with certain other medicines used to treat PAH.

2. What you need to know before you take Adempas

Do NOT take Adempas:
- if you are taking certain medicines called **PDE-5 inhibitors** (e.g. sildenafil, tadalafil, vardenafil). These are medicines used for the treatment of high blood pressure in the arteries of the lungs (PAH) or erectile dysfunction
- if you have **severe liver problems** (severe hepatic impairment, Child Pugh C)
- if you are **allergic** to riociguat or any of the other ingredients of this medicine (listed in section 6)
- if you are **pregnant**
- if you are taking **nitrates** or **nitric oxide donors** in any form, such as amyl nitrite ("recreational drugs"); medicines often used to treat high blood pressure, chest pain or heart disease.
- if you have **low blood pressure** (systolic blood pressure less than 95 mmHg) before starting first treatment with this medicine.

If any of these applies to you, **talk to your doctor first** and do not take Adempas.

Warnings and precautions
Talk to your doctor or pharmacist before taking Adempas if:
- you have recently experienced serious **bleeding from the lung**, or if you have undergone treatment to stop **coughing up blood** (bronchial arterial embolisation).
- you take **blood-thinning medicines** (anticoagulants) since this may cause bleeding from the lungs. Your doctor will regularly monitor you.
- you feel **short of breath** during treatment with this medicine, this can be caused by a build-up of fluid in the lungs. Talk to your doctor if this happens.
- you have **problems with your heart or circulation.**
- you are **older than 65 years**.
- your **kidneys do not work properly** (creatinine clearance < 30 ml/min) or if you are **on dialysis** as the use of this medicine is not recommended.
- you have **moderate liver problems** (hepatic impairment, Child Pugh B).
- you start or stop **smoking** during treatment with this medicine, because this may influence the level of riociguat in your blood.

You will receive Adempas only for special types of pulmonary arterial hypertension (PAH), see section 1. There is no experience in the use of Adempas in other types of PAH. Use of Adempas in other types of PAH is therefore not recommended. Your doctor will check if Adempas is suitable for you.

Children and adolescents
The use of Adempas in children and adolescents (under 18 years of age) should be avoided.

Other medicines and Adempas
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, in particular, medicines used for:
- high blood pressure or heart disease (such as nitrates and amyl nitrite) in any form, as you must not take those medicines together with Adempas.
- high blood pressure in the lung vessels (the pulmonary arteries), as you must not take certain medicines (sildenafil and tadalafil) together with Adempas. Other medications for high blood pressure in the lung vessels (PAH), such as bosentan and iloprost, can be used with Adempas, but you should still tell your doctor.
- erectile dysfunction (such as sildenafil, tadalafil, vardenafil), as you must not take those medicines together with Adempas.
- fungal infections (such as ketoconazole, itraconazole).

- HIV infection (such as ritonavir).
- epilepsy (e.g. phenytoin, carbamazepine, phenobarbitone).
- depression (St. John's Wort).
- preventing rejection of transplanted organs (ciclosporin).
- joint and muscular pain (niflumic acid).
- cancer (such as erlotinib, gefitinib).
- stomach disease or heartburn (antacids such as aluminium hydroxide/magnesium hydroxide). These antacid medicines should be taken at least two hours before or one hour after taking Adempas.
- nausea, vomiting (feeling or being sick) (such as granisetron).

Smoking
If you smoke, it is recommended that you stop, as smoking may reduce the effectiveness of these tablets. Please tell your doctor if you smoke or if you stop smoking during treatment.

Pregnancy and breast-feeding

Pregnancy
Do not take Adempas during pregnancy. If there is a chance you could become pregnant, use reliable forms of contraception while you are taking these tablets. You are also advised to take monthly pregnancy tests. 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 this medicine.

Breast Feeding
If you are breast-feeding or planning to breast-feed, ask your doctor or pharmacist for advice before taking this medicine because it might harm your baby. Your doctor will decide with you if you should stop breast-feeding or stop treatment with Adempas.

Driving and using machines
Adempas has moderate influence on the ability to drive and use machines. It may cause side effects such as dizziness. You should be aware of the side effects of this medicine before driving or using machines (see section 4).

Adempas contains lactose
If you have been told by a doctor that you have an intolerance to some sugars, tell your treating doctor before taking these tablets.

3. How to take Adempas

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 started and monitored by a doctor experienced in the treatment of CTEPH or PAH. During the first weeks of treatment your doctor will need to measure your blood pressure at regular intervals. Adempas is available in different strengths and by checking your blood pressure regularly at the beginning of your treatment, your doctor will ensure that you are taking the appropriate dose.

Dose
The recommended starting dose is a 1-mg tablet taken 3 times a day for 2 weeks.
The tablets should be taken 3 times a day, approximately 6 to 8 hours apart. They can generally be taken with or without food.
However, if you are prone to having low blood pressure (hypotension), you should not switch from taking Adempas with food to taking Adempas without food because it may affect how you react to this medicine.

Your doctor will increase the dose every 2 weeks to a maximum of 2.5 mg 3 times a day (maximum daily dose of 7.5 mg) unless you experience any side effects or very low blood pressure. In this case, your doctor will prescribe you Adempas at the highest dose you are comfortable on. For some patients lower doses three times a day might be sufficient, the optimal dose will be selected by your doctor.

Special considerations for patients with kidney or liver problems
You should tell your doctor if you have kidney or liver problems. Your dose may need to be adjusted. If you have severe liver problems (Child Pugh C), do not take Adempas.

65 years or older
If you are 65 years or older your doctor will take extra care in adjusting your dose of Adempas, because you may be at greater risk of low blood pressure.

Special considerations for patients who smoke
You should tell your doctor if you start or stop smoking during treatment with this medicine. Your dose may be adjusted.

If you take more Adempas than you should
If you have taken more tablets than you should and experience any side effects (see section 4), please contact your doctor. If your blood pressure drops (which can make you feel dizzy) then you may need immediate medical attention.

If you forget to take Adempas
Do not take a double dose to make up for a forgotten dose. If you miss a dose, continue with the next dose as planned.

If you stop taking Adempas
Do not stop taking this medicine without talking to your doctor first, because this medicine prevents the progression of the disease. If your treatment has to be stopped for 3 days or more, please tell your doctor before restarting your treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

The most **serious** side effects are:
- **coughing up blood** (common side effect)
- **acute bleeding from the lungs** may result in coughing up blood (uncommon side effect)**.**

If this happens, **contact your doctor immediately** as you may need urgent medical treatment.

Overall list of possible side effects:

Very common: may affect more than 1 in 10 people
- headache
- dizziness
- indigestion
- swelling of limbs
- diarrhoea
- feeling or being sick

Common: may affect up to 1 in 10 people
- inflammation in the digestive system
- reduction of red blood cells (anaemia) seen as pale skin, weakness or breathlessness
- awareness of an irregular, hard, or rapid heartbeat
- feeling dizzy or faint when standing up (caused by low blood pressure)
- coughing up blood
- nose bleed
- difficulty breathing through your nose
- pain in the stomach, intestine or abdomen
- heartburn
- difficulty in swallowing
- constipation
- bloating

Uncommon: may affect up to 1 in 100 people
- acute bleeding from the lungs. Contact your doctor immediately as you may need urgent medical treatment.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Adempas

Keep this medicine out of the sight and reach of children.

This medicine does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the blister and carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Adempas contains

- The **active substance** is riociguat.
  Each tablet contains 0.5 mg, 1 mg, 1.5 mg, 2 mg or 2.5 mg riociguat.

- The **other ingredients** are:
  Tablet core: cellulose microcrystalline, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and sodium laurilsulfate (see end of section 2 for further information on lactose).
  *Film-coat**:* hydroxypropylcellulose, hypromellose, propylene glycol and titanium dioxide (E 171).
  *1 mg, 1.5 mg, 2 mg and 2.5 mg tablets also have: ferric oxide yellow (E 172)
  *2 mg and 2.5 mg tablets also have: ferric oxide red (E 172)

What Adempas looks like and contents of the pack

Adempas is a film-coated tablet:
- *0.5 mg tablet:* white, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 0.5 and an “R” on the other side.

- *1 mg tablet:* pale yellow, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1 and an “R” on the other side.

- *1.5 mg tablet:* yellow-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1.5 and an “R” on the other side.

- *2 mg tablet:* pale orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2 and an “R” on the other side.

- *2.5 mg tablet:* red-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2.5 and an “R” on the other side.

They are available in packs of:
- 42 tablets: two transparent calendar blisters of 21 tablets each.
- 84 tablets: four transparent calendar blisters of 21 tablets each.
- 90 tablets: five transparent blisters of 18 tablets each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer Pharma AG
13342 Berlin
Germany

Manufacturer
Bayer Pharma AG
51368 Leverkusen
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder (the list of local representatives is located at the end of this booklet).

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.