1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.5 mg film-coated tablets
Adempas 1.0 mg film-coated tablets
Adempas 1.5 mg film-coated tablets
Adempas 2.0 mg film-coated tablets
Adempas 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains either 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg or 2.5 mg riociguat.

3. PHARMACEUTICAL FORM

Adempas 0.5 mg film-coated tablets:

White tablets marked with the Bayer cross on one side and 0.5 and an “R” on the other side.

Adempas 1.0 mg film-coated tablets:

Pale yellow tablets marked with the Bayer cross on one side and 1 and an “R” on the other side.

Adempas 1.5 mg film-coated tablets:

Yellow-orange tablets marked with the Bayer cross on one side and 1.5 and an “R” on the other side.

Adempas 2.0 mg film-coated tablets:

Pale orange tablets marked with the Bayer cross on one side and 2 and an “R” on the other side.

Adempas 2.5 mg film-coated tablets:

Red-orange tablets marked with the Bayer cross on one side and 2.5 and an “R” on the other side.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

Adempas is indicated for the treatment of adult patients with WHO functional Class II to III symptoms

- Inoperable CTEPH,
- Persistent or recurrent CTEPH after surgical treatment

to improve exercise capacity (see section 5.1.2).

Pulmonary arterial hypertension (PAH, WHO Group 1):

Adempas is indicated for the treatment of adult patients with WHO functional class II to III PAH to improve exercise capacity (see section 5.1.2).

Efficacy was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness included predominately patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

4.2.2 Dosage regimen

Adults

Treatment initiation

The recommended starting dose is 1.0 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart with or without food.

Dosage should be increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥95 mmHg and the patient has no signs or symptoms of hypotension. In some PAH patients, an adequate response on the 6 –minute walk distance (6MWD) may be reached at a dose of 1.5mg three times a day (see section 5.1) If systolic blood pressure falls below 95 mmHg dosage should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg, and the patient shows signs or symptoms of hypotension the current dose should be decreased by 0.5 mg three times a day .

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

Crushed tablets
For patients who are unable to swallow whole tablets, Adempas tablet may be crushed and mixed with water or soft foods such as applesauce immediately prior to use and administered orally *(see section 'Pharmacokinetic properties')*.

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.

4.2.3 Additional information on special populations

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

4.2.3.1 Transitioning to and from Adempas

Discontinue sildenafil at least 24 hours prior to administering Adempas. It is recommended to monitor for signs and symptoms of hypotension on initiation (see section '*Contraindications', 'Pharmacodynamic Interaction'* and *'Clinical efficacy'*).
Discontinue tadalafil at least 48 hours prior to administering Adempas. It is recommended to monitor for signs and symptoms of hypotension on initiation (see section '*Contraindications', 'Pharmacodynamic interaction'* and *'Clinical efficacy'*).
Discontinue Adempas at least 24 hours prior to administering a PDE5 inhibitor. It is recommended to monitor for signs and symptoms of hypotension on initiation (see section *'Contraindications', 'Pharmacodynamic Interaction'* and *'Clinical efficacy'*).

4.2.3.2 Pediatric patients

The safety and efficacy of Adempas have not yet been tested in patients below 18 years. No data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implication of these findings, the use of riociguat in children and in adolescents should be avoided.

4.2.3.3 Geriatric patients

In elderly (≥65 years) particular care should be exercised during individual dose titration.

4.2.3.4 Patients with hepatic impairment

Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to Adempas. Particular care should be exercised during individual dose titration.

Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of Adempas is not recommended in these patients *(see Section 'special warnings and precautions for use')*.

4.2.3.5 Patients with renal impairment

Patients with mild, moderate or severe renal impairment (creatinine clearance 80-15 mL/min) showed a higher exposure to Adempas. Particular care should be exercised during individual dose titration.

Patients with creatinine clearance <15 mL/min or on dialysis have not been studied and therefore use of Adempas is not recommended in these patients *(see section 'special warnings and precautions for use')*. There is a higher risk of hypotension in patients with renal impairment; therefore particular care should be exercised during individual dose titration.

4.2.3.6 Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors 20

Coadministration of Adempas 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) increases exposure to Adempas *(see section 'Interaction with other medicinal products and other forms of interaction*'). When initiating Adempas in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on Adempas doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see sections '*Dosage regimen*', '*Special warnings and precautions for use*' and '*Interaction with other medicinal products and other forms of interaction*').

4.2.3.7 Smoking status

Current smokers should be advised to stop smoking. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment of riociguat may be required in patients who stop or start smoking during treatment *(see section 'Interaction with other medicinal products and other forms of interaction')*.

4.3 Contraindications

Adempas is contraindicated during pregnancy *(see section 'pregnancy and lactation')*.

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (*see section 'Interaction with other medicinal products and other forms of interaction'*).

Co-administration of riociguat with PDE-5-inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated *(see section 'Interaction with other medicinal products and other forms of interaction').*

Co-administration of Adempas with other soluble guanylate cyclase stimulators is contraindicated (*see section* 'Interaction with other medicinal products and other forms of interaction').

Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) *(see section 'Pharmacodynamic properties').*

4.4 Special warnings and precautions for use

Pulmonary veno-occlusive disease

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

Respiratory tract bleeding

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

The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with Adempas, especially in the presence of risk factors, such as recent episodes of serious hemoptysis including those managed by bronchial arterial embolization. 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 withsubdural haematoma, haematemesis, and intra-abdominal haemorrhage.
The prescriber should regularly assess the benefit-risk with each individual patient.

Vasodilatory action:
Adempas has vasodilatory properties which may result in lowering of blood pressure. Before prescribing Adempas, physicians should carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g. patients on antihypertensive therapy or with resting hypotension, hypovolemia, severe left ventricular outflow obstruction or autonomic dysfunction).

Concomitant use with other medicinal products
The concomitant use of riociguat 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) results in a pronounced increase in riociguat exposure *(see section 'Interaction with other medicinal products and other forms of interaction).*

Assess the benefit-risk for each patient individually before prescribing Adempas in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors. Consider a starting dose of 0.5 mg Adempas, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment and consider a dose reduction for patients on Adempas doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see section 'Dosage and method of administration' and 'Interaction with other medicinal products and other forms of interaction').

In patients on stable doses of Adempas, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

The concomitant use of riociguat with strong CYP1A1 inhibitors, such as the tyrosine kinase inhibitor erlotinib, and strong P-gp/BCRP inhibitors, such as the immuno-suppressive agent cyclosporine A, may increase riociguat exposure *(see section 'Interaction with other medicinal products and other forms of interaction')*. These drugs should be used with caution. Blood pressure should be monitored and dose reduction of riociguat considered.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Pharmacokinetic Interactions

4.5.1.1 Effects of other substances on riociguat

Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP3A5, CYP2J2) oxidative metabolism, direct biliary/fecal excretion of the unchanged drug, and

renal excretion of the unchanged drug via glomerular filtration. Based on *in vitro* studies, riociguat was found to be a substrate for the membrane transport proteins P-gp/BCRP. Inhibitors or inducers of these enzymes or transporters may affect riociguat exposure.

Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors

Antifungals
In vitro, ketoconazole, classified as strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a 'multi-pathway CYP and P-gp/'breast cancer resistance protein' (BCRP) inhibitor' for riociguat metabolism and excretion. 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 Cmax. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h.

When initiating Adempas therapy in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. ketoconazole or itraconazole, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on Adempas doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension *(see section 'Dosage and method of administration', 'Special warnings and precautions for use'and 'Pharmacokinetic properties')*.

In patients on stable doses of Adempas, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Highly active antiretroviral therapy (HAART)
In *vitro*, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition, ritonavir showed inhibition of P-gp.

The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate 30% increase in mean Cmax. The safety profile observed in HIV patients taking a single dose of 0.5 mg riociguat together with different combinations of HIV drugs used in HAART was generally comparable to other patient populations.

When initiating Adempas treatment in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, e.g. as contained in HAART therapy, consider a starting dose of 0.5 mg riociguat, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on Adempas doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension *(see section 'Dosage and method of administration', 'Special warnings and precautions for use')*.

In patients on stable doses of Adempas, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Concomitant use with other CYP and P-gp/BCRP inhibitorsDrugs strongly inhibiting P-gp/BCRP such as the immuno-suppressive agent cyclosporine A, should be used with caution *(see section 'Special warnings and precautions for use')*.

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

Concomitant use with drugs increasing gastric pH

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 aluminum hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean C_{max} by 56% *(see section 'Dosage and method of administration')*. Antacids should be taken at least 1 hour after Adempas.

Concomitant use with CYP3A4 inducers

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% without compromising the efficacy of the combination *(see section 'Indications')*.

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.

4.5.1.2 Effects of Riociguat on other substances

Riociguat and its main metabolite are neither inhibitors nor inducers of major CYP isoforms (including CYP 3A4) or transporters (e.g. P-gp/BCRP) *in vitro* at therapeutic plasma concentrations.

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

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

4.5.2 Pharmacodynamic Interactions

Nitrates

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

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 hemodynamic effects. Doses above 1 mg riociguat were not investigated in this study.

A 12 week combination study in 18 patients with PAH on stable sildenafil treatment (20 mg three times daily) and riociguat (1.0 mg-2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part (non controlled) the concomitant use of sildenafil and riociguat resulted in a high rate of discontinuation, predominately due to hypotension. There was no evidence of a favorable clinical effect of the combination in the population studied.

Co-administration of riociguat with PDE-5-inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated *(see section 'Contraindications')*.

Soluble Guanylate Cyclase Stimulators
Co-administration of Adempas with other soluble guanylate cyclase stimulators is contraindicated (*see section* 'Contraindications').

Warfarin/Phenprocoumon

Concomitant treatment of riociguat and warfarin did not alter prothrombin time induced by the anticoagulant. The concomitant use of riociguat with other coumarin-derivates (e.g. phenprocoumon) is also not expected to alter prothrombin time.

Lack of mutual pharmacokinetic interactions between riociguat and the CYP2C9 substrate warfarin was demonstrated *in vivo*.

Acetyl salicylic acid
Riociguat did neither potentiate the bleeding time caused by acetyl salicylic acid nor affect the platelet aggregation in humans.

4.5.3 Food and dairy products

No clinically relevant interaction with food was observed.

4.5.4 Additional information on special populations

In cigarette smokers riociguat exposure is reduced by 50-60%. Therefore patients are advised to stop smoking *(see section 'Dosage and method of administration')*.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

There are no adequate data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity and development toxicity.

Therefore, Adempas is contraindicated during pregnancy (*see section 'Contraindications'*). Monthly pregnancy tests are recommended, and for one month after treatment discontinuation with Adempas.

4.6.2 Lactation

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

Because of the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy, taking into account the importance of the drug for the mother.

4.6.3 Fertility

4.6.4 Women of childbearing potential / Contraception

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

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The safety of Adempas has been evaluated in phase III trials of more than 650 patients with CTEPH or PAH receiving at least one dose of riociguat.

The safety profile of Adempas in both populations appeared to be similar, therefore adverse drug reactions (ADRs) identified from placebo controlled 12 and 16 weeks clinical trials are presented as pooled frequency in the table listed below (see Table 1).

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

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

Serious hemoptysis and pulmonary hemorrhage, including cases with fatal outcome have been observed in patients with CTEPH or PAH treated with Adempas *(see Section 'special warnings and precautions for use')*.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions observed with Adempas are represented in the table below.

They are classified according to System Organ Class (MedDRA). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention:

very common (≥ 1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),
very rare (< 1/10,000).

Table 1: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled CHEST 1 and PATENT 1 data)

System Organ Class (MedDRA)	Very Common	Common	Uncommon
Infections and infestations		Gastroenteritis	
Blood and the lymphatic system disorders		Anemia (incl. respective laboratory parameters)	
Nervous system disorders	Dizziness Headache		
Cardiac disorders		Palpitations	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Hemoptysis Epistaxis Nasal congestion	Pulmonary hemorrhage*
Gastrointestinal disorders	Dyspepsia Diarrhea Nausea Vomiting	Gastritis Gastrooesophageal reflux disease Dysphagia Gastrointestinal and abdominal pains Constipation Abdominal distension	
General disorders and administration site conditions	Edema peripheral		

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

4.9 Overdose

Inadvertent overdosing with total daily doses of 9-25 mg riociguat between 2-32 days was reported.

Adverse reactions were similar to those seen at lower doses *(see section 'Undesirable effects')*.

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

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

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

4.10 Special populations

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

4.10.1 Pediatric patients

The safety and efficacy of Adempas have not yet been tested in patients below 18 years. No data are available. Non-clinical data show an adverse effect on growing bone. Until more is known about the implications of these findings the use of riociguat in children and in adolescents should be avoided.

4.10.2 Geriatric patients

In elderly (≥65 years) particular care should be exercised during individual dose titration.

Elderly patients (≥65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 40% higher in elderly, mainly due to reduced (apparent) total and renal clearance.

4.10.3 Patients with hepatic impairment

Patients with mild hepatic impairment (Child Pugh A) had similar riociguat plasma concentrations compared to healthy controls.

Patients with moderate hepatic impairment (Child Pugh B) showed a higher exposure to Adempas. Particular care should be exercised during individual dose titration.

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

There was no clinically relevant change in exposure in cirrhotic subjects with mild-hepatic impairment (classified as Child Pugh A).

In cirrhotic subjects with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 50-70% compared to healthy controls.

There are no data in patients with severe hepatic impairment (classified as Child Pugh C), therefore use of Adempas is not recommended in these patients.

4.10.4 Patients with renal impairment

Patients with mild, moderate or severe renal impairment (creatinine clearance 80-15 mL/min) showed a higher exposure to Adempas. Particular care should be exercised during individual dose titration.

Patients with creatinine clearance <15 mL/min or on dialysis have not been studied and therefore use of Adempas is not recommended in these patients.There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Overall, mean dose- and weight- normalized exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function.

Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In individuals with mild (creatinine clearance 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 43%, 104% or 44%, respectively.

There are no data in patients with creatinine clearance <15 mL/min or on dialysis. Therefore use is not recommended in patients with creatinine clearance <15 mL/min or on dialysis.

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

4.10.5 Fertility, pregnancy and lactation

4.10.5.1 Pregnancy

There are no adequate data from the use of riociguat in pregnant women. Studies in animals have shown reproductive toxicity.
Therefore, Adempas is contraindicated during pregnancy.
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 8.1-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of 3.8- fold of human exposure (2.5 mg three times daily) abortion and fetal toxicity were seen.

4.10.5.2 Lactation

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

Because of the potential for serious adverse reactions in nursing infants Adempas should not be used during breast-feeding. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy, taking into account the importance of the drug for the mother.

4.10.5.3 Fertility

No specific studies with riociguat in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen.
In rats, no effects on male and female fertility were seen.

4.10.5.4 Women of childbearing potential / Contraception

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

4.10.6 Gender, Inter-Ethnic differences, Weight categories

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

4.10.7 Smoking status

Current smokers should be advised to stop smoking. Plasma concentrations of riociguat in smokers are reduced compared to non-smokers. Dose adjustment of riociguat may be required in patients who stop or start smoking during treatment.
In cigarette smokers riociguat exposure is reduced by 50-60%. Therefore patients are advised to stop smoking.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C02KX05

5.1.1 Mechanism of action/Pharmacodynamic effects

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 catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intra-cellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation.

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

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

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

5.1.2 Clinical efficacy

5.1.2.1 Efficacy in patients with chronic thrombolic pulmonary hypertension (CTEPH)

5.1.2.1.1 CHEST

Study design

A randomized, double-blind, multi-national, multi-center, placebo controlled phase III study (CHEST-1) was conducted in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Patients were included who are inoperable (assessed by an independent adjudication committee), or who have recurrent or persistent CTEPH after undergoing pulmonary endarterectomy (PEA).
The patient population included male and female patients between the age of 18 and 80. 72% of patients had inoperable CTEPH, 28% had recurrent or persisting CTEPH following PEA. The majority of patients had a World Health Organization (WHO) Functional Class II (31%) or III (64%) at baseline. The mean baseline six minute walking distance (6MWD) was 347 m. All patients were treatment naïve (PAH-specific medication was excluded).

CHEST-1 included 261 patients treated and valid for safety randomized to one of two treatment groups: Adempas individual dose titration (IDT) up to 2.5 mg tid (n=173, referred to as riociguat group), or placebo (n=88). During an 8-week titration phase, the dose of Adempas was titrated every 2-weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension. An individualized dose was reached at the end of the titration.

Efficacy endpoints:
All p-values are based on stratified Wilcoxon test (unless a different test is mentioned). All 95% CI and treatment effects are based on analysis of covariance (ANCOVA).
Primary endpoint:
The primary endpoint was the change from baseline at week 16 (last visit) in 6MWD compared to placebo.

Improvements in walking distance were apparent from week 2 onward, and at week 16 (n=261) the increase in 6MWD within the riociguat group was 46 m (95% Confidence Interval (CI): 25 m to 67 m; $p<0.0001$) compared to placebo (ITT analysis, see Table 2). Improvements of Adempas over placebo were observed in all sub-groups evaluated. Inoperable patients (n=189) demonstrated an increase in 6MWD of 54 m (95% CI: 29 m to 79 m), and patients with recurrent or persisting CTEPH following PEA (n=72) demonstrated an increase in 6MWD of 27 m (95% CI: -10 m to 63 m).

Table 2: **Effects of Adempas on 6MWD in CHEST-1 at week 16 (last visit; ITT analysis set)**

Entire patient population	**Adempas (IDT) (n=173)**	**Placebo (n=88)**
Baseline (m) [SD]	342 [82]	356 [75]
Change from baseline (m) [SD]	39 [79]	-6 [84]
Placebo-corrected difference (m) 95% CI ; [p-value]	46 25 m to 67 m; [<0.0001]	
Inoperable patient population	**Adempas (IDT) (n=121)**	**Placebo (n=68)**
Baseline (m) [SD]	335 [83]	351 [75]
Change from baseline (m) [SD]	44 [84]	-8 [88]
Placebo-corrected difference (m) 95% CI	54 29 m to 79 m	
Patient population with CTEPH post-PEA	**Adempas (IDT) (n=52)**	**Placebo (n=20)**
Baseline (m) [SD]	360 [78]	374 [72]
Change from baseline (m) [SD]	27 [68]	2 [73]
Placebo-corrected difference (m) 95% CI	27 -10 m to 63 m	

Secondary endpoints:

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

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

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

- NT-proBNP: Significantly reduced NT-proBNP (placebo-corrected mean change from baseline -444 ng/L, CI -843 to -45; see Table 3).

- WHO functional class: Significant improvement of at least one functional class in the riociguat group at week 16 (last visit) of 33% vs. 15% in the placebo group and a decline of at least one functional class was observed in 5% of patients in the riociguat group vs. 7% in the placebo group ($p = 0.0026$; see Table 4). Functional class was unchanged in 62% of patients in the riociguat group vs. 78% in the placebo group.

An effect in favor of the riociguat group (below threshold of hierarchical testing[1]) was shown for:

- Time to clinical worsening: Adempas-treated patients experienced a delay in time to clinical worsening versus placebo-treated patients (p = 0.1724; Stratified log-rank test). A trend towards lower incidence of clinical worsening events by week 16 (last visit) in patients treated with Adempas (2.3%) compared to placebo (5.7%) was observed (p = 0.2180, Mantel-Haenszel estimate, see Table 5, see Figure 1**)**.

- Borg CR 10 scale: Improvement in Borg CR 10 scale (-0.8 for Adempas vs. +0.2 for placebo, p = 0.0035).

- European quality of life (EQ-5D): Improvement in EQ-5D (change from baseline 0.13; 95% CI 0.06 to 0.21; p<0.0001).

- Living with Pulmonary Hypertension (LPH): Improvement of LPH (change from baseline -5.8; p = 0.1220; 95% CI -10.45 to -1.06).

Table 3: Effects of Adempas in CHEST-1 on PVR and NT-proBNP at week 16 (last visit)

Study Population	**Baseline [SD]**	**Change from Baseline [SD]**	**Placebo corrected difference**	**95% CI**	**p-value**
PVR (dyn*s*cm^{-5}) Adempas (IDT) (n=151)	791 [432]	-226 [248]	-246	-303 to -190	<0.0001
PVR (dyn*s*cm^{-5}) Placebo (n=82)	779 [401]	23 [274]	-	-	-
NT-proBNP (ng/L) Adempas (IDT) (n=150)	1508 [2338]	-291 [1717]	-444	-843 to -45	<0.0001
NT-proBNP (ng/L) Placebo (n=73)	1706 [2567]	76 [1447]	-	-	-

Table 4: **Effects of Adempas on the Change in Functional Class in CHEST-1 at week 16 (last visit; ITT analysis set)**

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

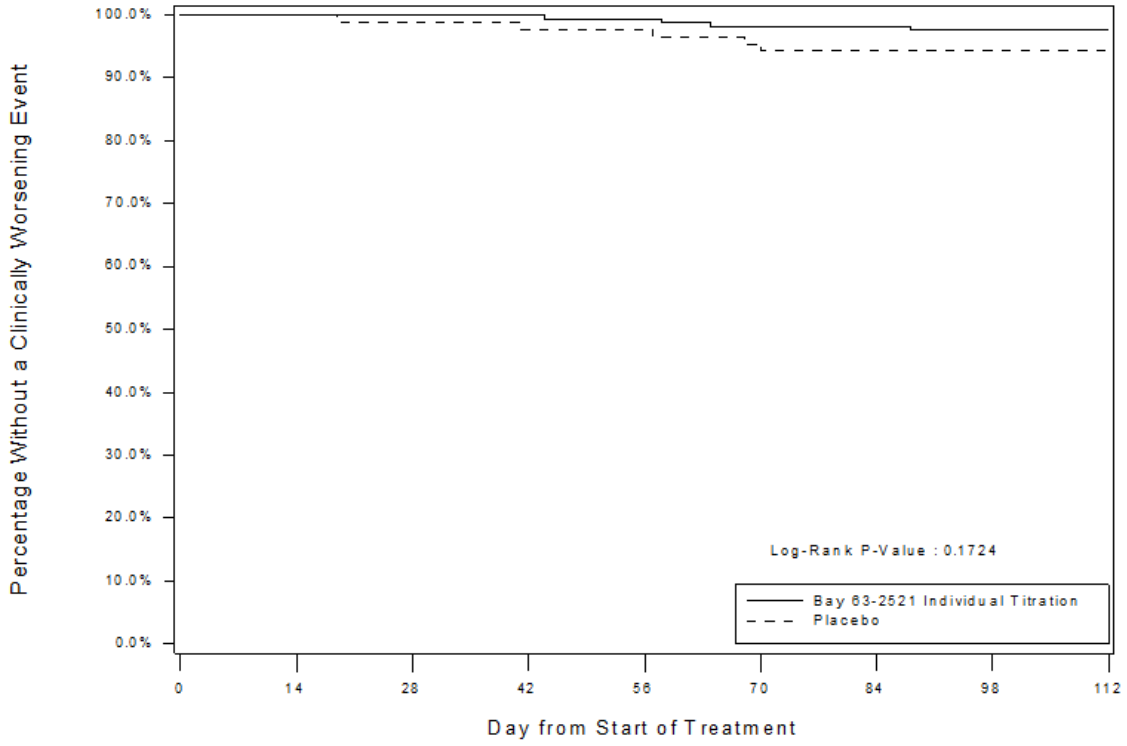
[1] All subsequent endpoints cannot be considered statistically significant in a formal sense because statistical significance was not achieved for time to clinical worsening in the hierarchical testing of the secondary efficacy variables.

Table 5: **Effects of Adempas in CHEST-1 on events of clinical worsening (ITT analysis set)**

Clinical Worsening Events	Adempas (IDT) (n=173)	Placebo (n=88)
Patients with any clinical worsening*	4 (2.3%)	5 (5.7%)
Death	2 (1.2%)	3 (3.4%)
Hospitalizations due to PH	0	1 (1.1%)
Decrease in 6MWD due to PH	1 (0.6%)	2 (2.3%)
Persistent worsening of FC due to PH	0	1 (1.1%)
Start of new PH treatment	2 (1.2%)	1 (1.1%)

* p-value = 0.2180 (Mantel-Haenszel estimate)
Note: Patients may have had more than one event of clinical worsening

Figure 1: CHEST-1 Kaplan-Meier plot for time to clinical worsening (Bay 63-2521 = Riociguat; ITT analysis set)



Hemodynamic parameters:

Right heart catheterization was performed at the beginning and the end of the placebo-controlled study period in 233 patients to generate a comprehensive set of cardiopulmonary hemodynamic data (see Table 6).

A statistically significant reduction of PVR (see above), mean pulmonary artery pressure (PAP_{mean}) (-5.0 mmHg, $p<0.0001$) and an increase in cardiac index (0.47 L/min/m^2;

p<0.0001) was shown in the riociguat group vs. placebo. The improvement seen for the hemodynamic variables describe above was also observed in other relevant hemodynamic parameters.

Table 6: CHEST-1, change in hemodynamic parameters from baseline to last visit: Comparison of riociguat 1.0-2.5 mg (RIO) and placebo (PBO) (ITT analysis set)

Parameter (unit)	Mean change		LS mean difference	95% CI	ANCOVA	Stratified Wilcoxon test
	RIO	PBO			p-value	p-value
PCWP (mmHg)	0.59	0.18	0.58	–0.36 to 1.53	0.2268	0.2285
RAP (mmHg)	–1.04	–0.55	–0.55	–1.72 to 0.62	0.3566	0.3593
PAPsyst (mmHg)	–6.84	0.95	–7.52	–10.88 to –4.16	<0.0001	<0.0001
PAPdiast (mmHg)	–3.05	0.67	–3.62	–5.30 to –1.95	<0.0001	0.0002
PAPmean (mmHg)	–4.31	0.76	–4.96	–6.75 to –3.16	<0.0001	<0.0001
MAP (mmHg)	–9.27	–0.29	–9.15	–11.83 to –6.46	<0.0001	<0.0001
SvO_2 (%)	2.95	–0.44	3.85	1.46 to 6.25	0.0017	0.0010
CO (L/min)	0.81	–0.03	0.86	0.59 to 1.12	<0.0001	<0.0001
CI ($L/min/m^2$)	0.45	–0.01	0.47	0.33 to 0.62	<0.0001	<0.0001
PVR* ($dyn*s*cm^{-5}$)	–226	23.1	–246.43	–303.33 to –189.53	<0.0001	<0.0001
PVRI ($dyn*s*cm^{-5}*m^2$)	–397	48.3	–448.95	–553.62 to –344.27	<0.0001	<0.0001
SVR ($dyn*s*cm^{-5}$)	–445	16.6	–478.24	–602.30 to –354.19	<0.0001	<0.0001
SVRI ($dyn*s*cm^{-5}*m^2$)	–799	53.7	–914.16	–1140.97 to –687.35	<0.0001	<0.0001

* PVR was a secondary endpoint in the study

All other parameters were not pre-specified as endpoints

Long-term treatment of CTEPH

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. At the end of the study, mean (SD) treatment duration in the total group was 1285 (709) days and median duration was 1174 days (ranging from 15 to 3512 days). In total, 221 (93.2%) patients had a treatment duration of approximately 1 year (at least 48 weeks), 205 (86.5%) patients of approximately 2 years (at least 96 weeks) and 142 (59.9%) patients of approximately 3 years (at least 144 weeks). Treatment exposure was 834 person years in total.

The safety profile in CHEST-2 was similar to that observed in pivotal trials. After treatment with Adempas, the mean 6MWD improved in the overall population by 53 m at 12 months (n=208), 48m at 24 months (n=182), and 49 m at 36 months (n=117) compared to baseline.

Improvements in 6MWD persisted until the end of the study.

Table 7 shows the proportion of patients* with changes in WHO functional class during Adempas treatment compared to baseline.

Table 7: CHEST-2: Changes in WHO Functional

	Changes in WHO Functional Class (n (%) of patients)

Treatment duration in CHEST-2	Improved	Stable	Worsened
1 years (n=217)	100 (46%)	109 (50%)	6 (3%)
2 years (n=193)	76 (39%)	111 (58%)	5 (3%)
3 years (n=128)	48 (38%)	65 (51%)	14 (11%)
*Patients participated in the study until the drug was approved and commercially available in their countries			

The probability of survival at 1-year was 97%, at 2 years 93% and at 3 years 89%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 90% respectively, and for patients of WHO functional class III at baseline was 97%, 93% and 88% respectively. Without a control group, however, these data must be interpreted cautiously.

5.1.2.2 Efficacy in patients with pulmonary arterial hypertension (PAH)

5.1.2.2.1 Patent

Study design

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

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

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

PATENT-1 included 443 patients treated and valid for safety, randomized to one of three treatment groups: Adempas individual dose titration up to 2.5 mg tid (n=254); placebo (n=126); and a "capped" dose titration up to 1.5 mg tid (n=63; exploratory dose arm, no statistical testing performed). During an 8-week titration phase, the dose of Adempas was titrated every 2 weeks based on the patient's systolic blood pressure and signs or symptoms of hypotension. An individualized dose was reached at the end of the titration.

Efficacy endpoints:

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

Primary endpoint:

The primary endpoint was the change from baseline at week 12 (last visit) in six minutes walking distance (6MWD) compared to placebo.

Improvements in walking distance were apparent from week 2 onward, and at week 12 for the riociguat group was 36 m (95% Confidence Interval (CI): 20 m to 52 m; $p<0.0001$) compared to placebo (ITT analysis, see Table 8). Improvements of Adempas over placebo were observed in all sub-groups evaluated. Treatment-naïve patients (n=189) demonstrated an increased 6MWD of 38 m (95% (CI): 14 m to 62 m).
Pre-treated patients (n=191) demonstrated an increased 6MWD of 36 m (95% CI: 15 m to 56 m). Further subgroup analysis of patients pre-treated with ERAs (n=167) revealed a treatment effect estimate of 26 m, (95% CI: 5 m to 46 m). In patients pre-treated with

prostacyclin analogues (n=27[2]), the estimated treatment effect was 101 m, (95% CI: 27 m to 176 m).

Table 8: **Effects of Adempas on 6MWD in PATENT-1 at week 12 (last visit; ITT analysis set)**

Entire patient population	**Adempas (IDT) (n=254)**	**Placebo (n=126)**
Baseline (m) [SD]	361 [68]	368 [75]
Change from baseline (m) [SD]	30 [66]	-6 [86]
Placebo-corrected difference (m) 95% CI, [p-value]	36 20 m to 52 m, [<0.0001]	
Treatment-naïve patient population	**Adempas (IDT) (n=123)**	**Placebo (n=66)**
Baseline (m) [SD]	370 [66]	360 [80]
Change from baseline (m) [SD]	32 [74]	-6 [88]
Placebo-corrected difference (m) 95% CI	38 14 m to 62 m	
Pre-treated patient population	**Adempas (IDT) (n=131)**	**Placebo (n=60)**
Baseline (m) [SD]	353 [69]	376 [68]
Change from baseline (m) [SD]	27 [58]	-5 [83]
Placebo-corrected difference (m) 95% CI	36 15 m to 56 m	

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

Secondary endpoints:

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

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

- Pulmonary vascular resistance (PVR): Significantly reduced PVR (p<0.0001, placebo-corrected mean change from baseline of -226 dyn*s*cm^{-5}; 95% CI -281 to -170; p<0.0001; see Table 9).
- NT-proBNP: Significantly reduced NT-proBNP (placebo-corrected mean change from baseline -432 ng/L, 95% CI -782 to -82; see Table 9).
- WHO functional class: Significant improvement of at least one functional class in the riociguat group at week 12 (last visit) of 21% vs. 14% in the placebo group and a

decline of at least one functional class was observed in 4% of patients in the riociguat group vs. 14% in the placebo group (p = 0.0033; see Table 10). Functional class was unchanged in 76% of patients in the riociguat group vs. 71% in the placebo group.

- Time to clinical worsening: Adempas-treated patients experienced a significant delay in time to clinical worsening versus placebo-treated patients (p = 0.0046; Stratified log-rank test). Significantly fewer events of clinical worsening up to week 12 (last visit) were observed in patients treated with Adempas (1.2%) compared to placebo (6.3%) (p = 0.0285, Mantel-Haenszel estimate, see Table 11, see Figure 2).

- Borg CR 10 scale: Significant improvement in Borg CR 10 scale (-0.4 for Adempas vs. +0.1 for placebo, p = 0.0022; see Table 9).

An effect in favor of the riociguat group (below threshold of hierarchical testing[3]) was shown for patients´ well-being in terms of:

- European quality of life (EQ-5D): Change from baseline 0.06 (95% CI 0.01 to 0.11; p = 0.0663).

- Living with Pulmonary Hypertension (LPH): Improvement in LPH (change from baseline -6.2; p = 0.0019; 95% CI -9.8 to -2.5).

Table 9: Effects of Adempas in PATENT-1 on PVR, NT-proBNP and Borg CR 10 scale at week 12 (last visit)

Study Population	Baseline [SD]	Change from Baseline [SD]	Placebo corrected difference	95% CI	p-value
PVR (dyn*s*cm^{-5}) Riociguat (IDT) (n=232)	791 [453]	-223 [260]	-226	-281 to -170	<0.0001
PVR (dyn*s*cm^{-5}) Placebo (n=107)	834 [477]	-9 [317]	-	-	-
NT-proBNP (ng/L) Adempas (IDT) (n=228)	1027 [1799]	-198 [1721]	-432	-782 to -82	<0.0001
NT-proBNP (ng/L) Placebo (n=106)	1228 [1775]	232 [1011]	-	-	-
Borg CR 10 Scale Adempas (IDT) (n=254)	3.9 [2.2]	-0.4 [1.7]	-	-	0.0022
Borg CR 10 Scale Placebo (n=126)	3.9 [2.5]	0.09 [2.1]	-	-	-

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

Table 10: **Effects of Adempas on the change in Functional Class in PATENT-1 at week 12 (last visit; ITT analysis set)**

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

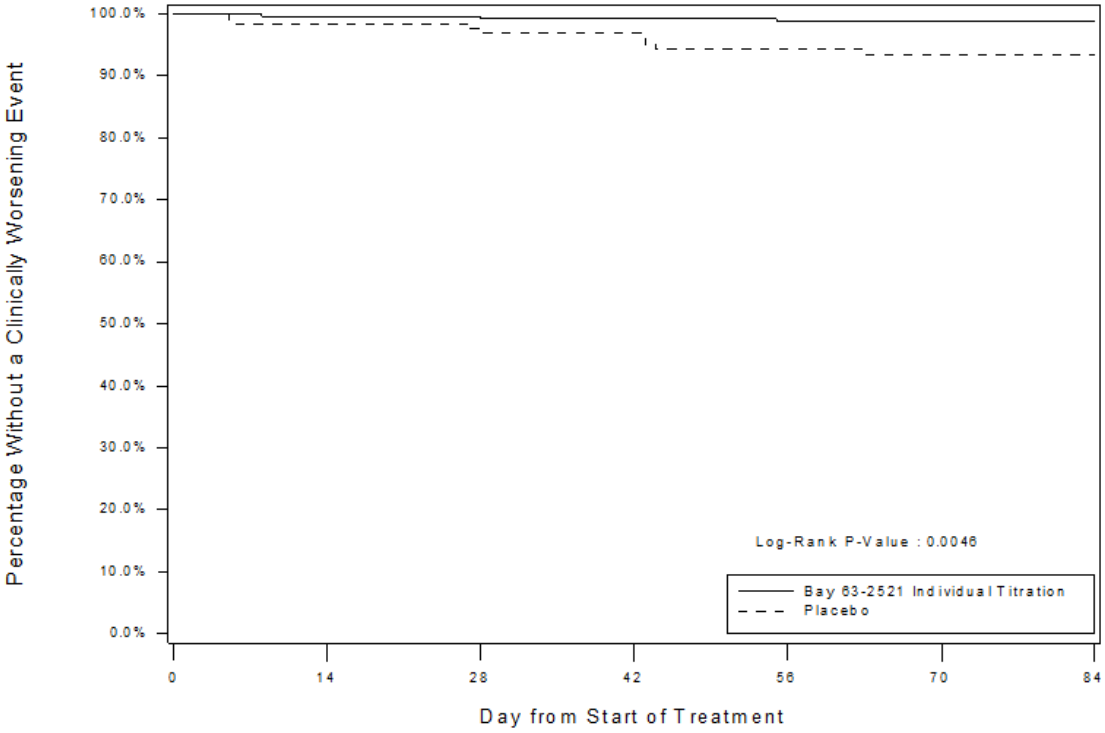
Table 11: **Effects of Adempas in PATENT-1 on events of clinical worsening (ITT analysis set)**

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

* p-value = 0.0285 (Mantel-Haenszel estimate)

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

Figure 2: PATENT-1 Kaplan-Meier plot for time to clinical worsening (Bay 63-2521 = Riociguat; ITT analysis set)



Hemodynamic parameters:

Right heart catheterization was performed at the beginning and the end of the placebo-controlled study period in 339 patients to generate a comprehensive set of cardiopulmonary hemodynamic data (see Table 12).

A statistically significant reduction of PVR (see above), mean pulmonary artery pressure (PAP_{mean}) (-3.8 mmHg¸ $p<0.0001$) and an increase in cardiac index (0.56 L/min/m^2; $p<0.0001$) was shown in the riociguat group vs. placebo. The improvement seen for the hemodynamic variables describe above was also observed in other relevant hemodynamic parameters.

Table 12: PATENT-1, change in hemodynamic parameters from baseline to last visit: Comparison of riociguat 1.0-2.5 mg (RIO) and placebo (PBO) - ITT analysis set

Parameter (unit)	Mean change		LS mean difference	95% CI	ANCOVA	Stratified Wilcoxon test
	RIO	PBO			p-value	p-value
PCWP (mmHg)	1.08	0.46	0.41	–0.36 to 1.18	0.2972	0.0830
RAP (mmHg)	–0.20	0.97	–1.01	–2.15 to 0.13	0.0832	0.0734
PAPsyst (mmHg)	–5.39	0.78	–6.73	–9.43 to –4.04	<0.0001	<0.0001
PAPdiast (mmHg)	–3.19	–1.12	–2.41	–4.15 to –0.68	0.0066	0.0110
PAPmean (mmHg)	–3.93	–0.50	–3.83	–5.61 to –2.06	<0.0001	0.0002
MAP (mmHg)	–8.54	–1.40	–7.25	–9.60 to –4.90	<0.0001	<0.0001
SvO_2 (%)	3.15	–2.33	5.02	3.20 to 6.84	<0.0001	<0.0001
CO (L/min)	0.93	–0.01	0.93	0.70 to 1.15	<0.0001	<0.0001
CI (L/min/m^2)	0.54	–0.02	0.56	0.44 to 0.69	<0.0001	<0.0001
PVR* (dyn*s*cm^{-5})	–223	–8.9	–225.72	–281.37 to –170.08	<0.0001	<0.0001
PVRI (dyn*s*cm^{-5}*m^2)	–374	–22.4	–376.81	–468.90 to –284.72	<0.0001	<0.0001
SVR (dyn*s*cm^{-5})	–448	–67.5	–394.57	–472.95 to –316.19	<0.0001	<0.0001
SVRI (dyn*s*cm^{-5}*m^2)	–753	–130	–675.31	–800.84 to –549.79	<0.0001	<0.0001

* PVR was a secondary endpoint in the study

All other parameters were not pre-specified as endpoints

Long-term treatment of PAH

An open label extension study (PATENT-2) included 396 patients who had completed PATENT-1. In PATENT-2, mean (SD) treatment duration in the total group (not including exposure in PATENT-1) was 1375 (772) days and median duration was 1331 days (ranging from 1 to 3565). In total, treatment exposure was approximately 1 year (at least 48 weeks) for 90%, 2years (at least 96 weeks) for 85%, and 3 years (at least 144 weeks) for 70% of patients. Treatment exposure was 1491 person years in total.

The safety profile in PATENT-2 was similar to that observed in pivotal trials. Aftertreatment with Adempas, the mean 6MWD improved in the overall population by 50m at 12 months (n=347), 46 m at 24 months (n=311) and 46 m at 36 months (n=238) compared to baseline. Improvements in 6MWD persisted until the end of study. Table 13 shows the proportion of patients* with changes in WHO functional class during Adempas treatment compared to baseline.

Table 13: PATENT-2: Changes in WHO Functional Class

	Changes in WHO Functional Class (n(%) of patients)		
Treatment duration in PATENT-2	Improved	Stable	Worsened
1 years (n=358)	116 (32%)	222 (62%)	20 (6%)
2 years (n=321)	106 (33%)	189 (59%)	26 (8%)
3 years (n=257)	88 (34%)	147 (57%)	22 (9%)
*Patients participated in the study until the study drug was approved and commercially available in their countries.			

The probability of survival at 1-year was 97%, at 2 years 93% and at 3 years 88%.Survival in

patients of WHO functional class II at baseline at 1,2 and 3 years was 98%,96% and 93% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 84% respectively. Without a control group, however, these data must be interpreted cautiously.

5.1.2.2.2 RESPITE

Study in PAH patients transitioned from PDE5 inhibitors to Adempas

A 24-week, multicenter, open-label study was conducted in 61 adult PAH patients stable on sildenafil (n=40) or tadalafil (n=21) for at least 90 days; 82% of these patients received background therapy with an endothelin receptor antagonist. Patients included in the study were WHO Functional Class III and hemodynamically stable at baseline. All patients in the study were transitioned from sildenafil or tadalafil to Adempas (median treatment-free time of 1 day for sildenafil and 3 days for tadalafil) *(see section 'Contraindications')*.

Fifty-one patients (84%) completed the study, and 92% of completers were receiving treatment with 2.5 mg 3 times daily at Week 24. Six patients (10%) experienced at least one clinical worsening event during the study, including 2 deaths unrelated to study drug. No serious adverse events were reported during the transition period. Overall, the safety profile observed in the study was comparable with that observed in the pivotal trials. Changes observed in patients who completed the study after 24 weeks are reported in Table 14. Without a control group the data should be interpreted cautiously.

Effects of Adempas in Patients Transitioned from PDE5 Inhibitors

Table 14: **Effects of Adempas in Patients Transitioned from PDE5 Inhibitors**

Parameter, mean (SD)	Baseline**		Week 24		Change from baseline to Week 24***
	n*	Value	n*	Value	
6MWD, m	61	357 (81)	51	395 (100)	+31 (63)
WHO FC I/II/III/IV, %	61	0/0/100/0	52	2/52/46/0	—
NT-proBNP, pg/mL	60	1190 (1828)	52	737 (1104)	–347 (1235)
PVR, dyn·s·cm–5	61	835 (272)	49	753 (379)	–103 (296)
Cardiac index, L/min/m^2	61	2.3 (0.4)	48	2.6 (0.6)	+0.3 (0.5)
mPAP, mmHg	61	51.8 (11.9)	49	49.7 (13.2)	–2.8 (8.8)
* Numbers of patients for which measurements are available ** Baseline: last documented value while still receiving PDE5 Inhibitor; data are mean (SD) *** Change from baseline for patients with data available at baseline and Week 24					

5.1.2.3 Long-term safety in PAH and CTEPH in a real-world setting

The post approval safety study EXPERT was a global, multicenter, prospective, uncontrolled, noninterventional
cohort study that included 1282 riociguat treated patients with CTEPH (n=956) and
PAH (n=326) to further investigate long-term drug safety in real-life clinical practice. Total drug exposure was 1898 person-years. An observation period of at least 21 months was reported for 794/1282 patients (61.9%).
The results of EXPERT are consistent with the existing safety profile of riociguat from previous clinical studies for PAH and CTEPH.

5.1.2.4 Adverse Effects in Pulmonary hypertension associated with idiopathic interstitial pneumonias (WHO Group 3)

A randomized, double blind, placebo-controlled study in patients with pulmonary hypertension

associated with idiopathic interstitial pneumonias (PH-IIP, WHO Group 3) compared riociguat (73) to placebo (74). The study was terminated prematurely due to increased risk of mortality and serious adverse events in patients treated with riociguat and a lack of efficacy. More patients taking riociguat died (11% vs. 4%) and had serious adverse events (37% vs. 23%) during the main phase. In the long-term extension, more patients who switched from the placebo group to riociguat (21%) died than those who continued in the riociguat group (3%).
Riociguat is therefore contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias *(see section 'Contraindications')*.

5.2 Pharmacokinetic properties

5.2.1 Absorption

The absolute bioavailability of riociguat is high (94%). Riociguat is rapidly absorbed with maximum concentrations (Cmax) appearing 1-1.5 hours after tablet intake.
Intake with food does not affect riociguat AUC. Cmax was reduced to a minor extent (35% lowering). This is not considered clinically relevant. Therefore riociguat can be taken with or without food.

Bioavailability (AUC and Cmax) is comparable for Adempas administered orally as a crushed tablet suspended in applesauce or in water compared to a whole tablet *(see section 'Method of administration').*

5.2.2 Distribution

Plasma protein binding in humans is high at approximately 95%, with serum albumin and α1-acidic glycoprotein being the main binding components.
The volume of distribution is moderate with volume of distribution at steady state being approximately 30 L.

5.2.3 Metabolism / Biotransformation

N-demethylation, catalyzed by CYP 1A1, CYP 3A4, CYP3A5 and CYP 2J2, is the major biotransformation pathway of riociguat leading to its major circulating active metabolite (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolized to the pharmacologically inactive N-glucuronide.

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

5.2.4 Elimination / Excretion

Total riociguat (parent compound and metabolites) is excreted via both renal (33-45%) and biliary/fecal routes (48-59%). Approximately 4 to 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 feces.
Based on in vitro data riociguat and its main metabolite are substrates of the transporter proteins P-gp (P-glycoprotein) and BCRP (breast cancer resistance protein).
With a systemic clearance of about 3-6 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.

5.2.5 Linearity / Non-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%.

5.2.6 Additional information on special populations

5.2.6.1 Geriatric patients

Elderly patients (≥65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 40% higher in elderly, mainly due to reduced (apparent) total and renal clearance (*see section 'Dosage regimen'*).

5.2.6.2 Patients with hepatic impairment

There was no clinically relevant change in exposure in cirrhotic subjects with mild-hepatic impairment (classified as Child Pugh A).

In cirrhotic subjects with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 50-70% compared to healthy controls (*see section 'Dosage regimen')*.
There are no data in patients with severe hepatic impairment (classified as Child Pugh C), therefore use of Adempas is not recommended in these patients (*see section 'Dosage regimen', 'Special warnings and precautions for use'*).

5.2.6.3 Patients with renal impairment

Overall, mean dose- and weight- normalized exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function. Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In individuals with mild (creatinine clearance 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 43%, 104% or 44%, respectively (*see section 'Dosage regimen')*.
There are no data in patients with creatinine clearance <15 mL/min or on dialysis. Therefore use is not recommended in patients with creatinine clearance <15 mL/min or on dialysis (*see section 'Dosage regimen' and 'Special warnings and precautions for use')*.

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

5.2.6.4 Gender, Inter-Ethnic differences, Weight categories

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

5.2.6.5 Pharmacokinetic / Pharmacodynamic relationships

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

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 (hemodynamic and smooth muscle relaxing effects). In fast growing, adolescent rats, effects on bone formation were seen. In juvenile rates, 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 after administration of riociguat to adult rats.

In rats, no effects on male and female fertility were seen.

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 8.1-fold of human exposure (2.5 mg three times daily). In rabbits, starting at systemic exposure of 3.8- fold of human exposure (2.5 mg three times daily) abortion and fetal toxicity were seen.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

- cellulose microcrystalline
- crospovidone
- hypromellose 5cP
- lactose monohydrate
- magnesium stearate
- sodium laurilsulphate

Film coat:

0.5 mg tablets:

- hydroxypropylcellulose
- hypromellose 3cP
- propylene glycol
- titanium dioxide (E 171)

1.0 mg, 1.5 mg tablets:

- hydroxypropylcellulose
- hypromellose 3cP
- propylene glycol
- titanium dioxide (E 171)
- ferric oxide yellow (E 172)

2.0 mg and 2.5 mg tablets:

- hydroxypropylcellulose
- hypromellose 3cP
- 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

Please refer to labels

6.4 Special precautions for storage

Store at or below 30 ° C

6.5 Nature and contents of container

Foil 300 µm PP colorless transparent (0110) sealed with Foil 20 µm Al sealable to PP (0202 | 0248)

6.6 Instructions for use / handling

None

6.7 Presentation

0.5mg, 1mg, 1.5mg, 2.0mg and 2.5mg tablets are available in packs of 42 tablets consisting of two transparent calendar blisters of 21 tablets each.

Not all presentations may be marketed.

Manufactured by:
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

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