ADEMPAS®

Film-coated Tablet

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 and 2.5 mg riociguat.
For the full list of excipient(s) see section 'list of excipients'.

3. PHARMACEUTICAL FORM

Adempas 0.5 mg film-coated tablets:
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.
Adempas 1.0 mg film-coated tablets:
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.
Adempas 1.5 mg film-coated tablets:
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.
Adempas 2.0 mg film-coated tablets:
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.
Adempas 2.5 mg film-coated tablets:
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 80 - 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.

Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors
When initiating Adempas in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, such as azole antimycotics (e.g. ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir), 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 4.4 and 4.5).

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.

Crushed tablets
For patients who are unable to swallow whole tablets, Adempas tablets may be crushed and mixed with water or soft foods such as applesauce immediately prior to use and administered orally (see section 5.2).

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.
- Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) (see Section 5.1)
- Co-administration of Adempas with other soluble guanylate cyclase stimulators is contraindicated (see section 4.5).

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 benefitrisk 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.

Pregnancy/contraception

Adempas is contraindicated during pregnancy (see section 4.3). Therefore, female patients at potential risk of pregnancy must use an effective method of contraception. Monthly pregnancy tests are recommended.

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, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) results in a pronounced increase in riociguat exposure (see sections 4.5 and 5.2).
- 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. To mitigate the risk of

hypotension, consider dose reduction and monitoring for signs and symptoms of hypotension (see sections 4.2 and 4.5).

- 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-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 . 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

Adempas film coated tablet contains 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).

Soluble Guanylate Cyclase Stimulators
Co-administration of Adempas with other soluble guanylate cyclase stimulators 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, CYP3A5, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of unchanged riociguat and renal excretion of unchanged riociguat via glomerular filtration.

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

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 C_{max}. 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.

To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, e.g. as contained in HAART, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and , 4.4).

Antifungals

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.

To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, e.g. ketoconazole, posaconazole or itraconazole consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).

Concomitant use with other CYP and P-gp/BCRP inhibitors

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).

Concomitant use with medicinal products 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 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.

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% (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 or 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

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 difference (m) 95% CI	27 -10 to 63	

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·s·cm^{-5}) [SD]	790.7 [431.6]	779.3 [400.9]
Mean change from baseline (dyn·s·cm^{-5}) [SD]	-225.7 [247.5]	23.1 [273.5]
Placebo-adjusted difference (dyn·s·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 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 from15 to 3512 days). In total, 221 patients (93.2%) had a treatment duration of approximately 1 year (at least 48 weeks), 205 patients (86.5%) of approximately 2 years (at least 96 weeks) and 142 patients (59.9%) 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 riociguat, the mean 6MWD improved in the overall population by 53 m at 12 months

(n=208), 48 m 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 4 shows the proportion of patients* with changes in WHO functional class during riociguat treatment compared to baseline.

Table 4: CHEST-2: Changes in WHO Functional Class

	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 was 97% after 1 year, 93% after to 2 years and 89% after 3 years of riociguat treatment.

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 5). 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 5: 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 6).

Table 6: 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 ($dyn \cdot s \cdot cm^{-5}$) 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 7).

Table 7: 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 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 days). In total, treatment exposure was approximately 1 year (at least 48 weeks) for 90%, 2 years (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. After treatment with riociguat, the mean 6MWD improved in the overall population by 50 m 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 the study.
Table 8 shows the proportion of patients* with changes in WHO functional class during riociguat treatment compared to baseline.

Table 8: 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 was 97% after 1 year, 93% after 2 years and 88% after 3 years of riociguat treatment.

5.1.2.3 Long-term safety in PAH and CTEPH in a real-world setting
The post approval safety study EXPERT 77 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.

Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

A randomised, double blind, placebo-controlled phase II study (RISE-IIP) to evaluate the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension

associated with idiopathic interstitial pneumonias (PH-IIP) was terminated early, due to an increased risk of mortality and serious adverse events in patients treated with riociguat and 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 4.3).

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%.

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 4.2).

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, CYP3A5 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 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 below 30° C

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 14 or 56 film-coated tablets.
Not all pack sizes may be marketed.

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