

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Adempas 0.5 mg film-coated tablets

Each film-coated tablet contains 0.5 mg of riociguat.

Adempas 1 mg film-coated tablets

Each film-coated tablet contains 1 mg of riociguat.

Adempas 1.5 mg film-coated tablets

Each film-coated tablet contains 1.5 mg of riociguat.

Adempas 2 mg film-coated tablets

Each film-coated tablet contains 2 mg of riociguat.

Adempas 2.5 mg film-coated tablets

Each film-coated tablet contains 2.5 mg of riociguat.

Excipient with known effect

Adempas 0.5 mg film-coated tablets

Each 0.5 mg film-coated tablet contains 37.8 mg lactose (as monohydrate).

Adempas 1 mg film-coated tablets

Each 1 mg film-coated tablet contains 37.2 mg lactose (as monohydrate).

Adempas 1.5 mg film-coated tablets

Each 1.5 mg film-coated tablet contains 36.8 mg lactose (as monohydrate).

Adempas 2 mg film-coated tablets

Each 2 mg film-coated tablet contains 36.3 mg lactose (as monohydrate).

Adempas 2.5 mg film-coated tablets

Each 2.5 mg film-coated tablet contains 35.8 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

- *0.5 mg tablet*: white, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 0.5 and an “R” on the other side.
- *1 mg tablet*: pale yellow, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1 and an “R” on the other side.
- *1.5 mg tablet*: yellow-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1.5 and an “R” on the other side.
- *2 mg tablet*: pale orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2 and an “R” on the other side.

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

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, treatment should be restarted with 1 mg three times daily for 2 weeks, and continued with the dose titration regimen as described above.

Transitioning between phosphodiesterase-5 (PDE5) inhibitors and riociguat

Sildenafil must be discontinued at least 24 hours prior to administration of riociguat.

Tadalafil must be discontinued at least 48 hours prior to administration of riociguat.

Riociguat must be discontinued at least 24 hours prior to administration of a PDE5 inhibitor.

It is recommended to monitor for signs and symptoms of hypotension after any transition (see sections 4.3, 4.5 and 5.1).

Special populations

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

Elderly

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 medicinal product (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 mild and moderate renal impairment (creatinine clearance <80 - 30 mL/min) showed a higher exposure to this medicinal product (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).

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 undesirable effects 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.

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 sections 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 apple sauce, immediately prior to use and administered orally (see section 5.2).

4.3 Contraindications

- Co-administration with PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) (see sections 4.2 and 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 sections 4.4; 4.5 and 4.6).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers' (see section 4.5).
- Concomitant use with other soluble guanylate cyclase stimulators.
- 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)

4.4 Special warnings and precautions for use

In pulmonary arterial hypertension, studies with riociguat have been mainly performed in forms related to idiopathic or heritable PAH and PAH associated with connective tissue disease. The use of riociguat in other forms of PAH not studied is not recommended (see section 5.1).

In chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy is the treatment of choice as it is a potentially curative option. According to standard medical practice, expert assessment of operability should be done prior to treatment with riociguat.

Pulmonary veno-occlusive disease

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

Respiratory tract bleeding

In pulmonary hypertension patients there is increased likelihood for respiratory tract bleeding, particularly among patients receiving anticoagulation therapy. A careful monitoring of patients taking anticoagulants according to common medical practice is recommended.

The risk of serious and fatal respiratory tract bleeding may be further increased under treatment with riociguat, especially in the presence of risk factors, such as recent episodes of serious haemoptysis including those managed by bronchial arterial embolisation. Riociguat should be avoided in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation.

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

Hypotension

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

Riociguat must not be used in patients with a systolic blood pressure below 95 mmHg (see section 4.3). Patients older than 65 years are at increased risk of hypotension. Therefore, caution should be exercised when administering riociguat in these patients.

Renal impairment

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

Hepatic impairment

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

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

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 CYP and P-gp / 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 sections 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.

Adempas contains lactose

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

Adempas contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”.

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, including recreational drugs called ‘poppers’, is contraindicated (see section 4.3).

PDE5 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 PDE5 inhibitors (such as sildenafil, tadalafil, vardenafil) is contraindicated (see sections 4.2 and 4.3).

RESPITE was a 24-week, uncontrolled study to investigate switching from PDE5 inhibitors to riociguat, in 61 adult PAH patients on stable PDE5 inhibitors. All patients were WHO Functional Class III and 82% received background therapy with an endothelin receptor antagonist (ERA). For the transition from PDE5 inhibitors to riociguat, median treatment-free time for sildenafil was 1 day and for tadalafil 3 days. Overall, the safety profile observed in the study was comparable with that observed in the pivotal trials, with no serious adverse events reported during the transition period. Six patients (10%) experienced at least one clinical worsening event, including 2 deaths unrelated to study drug. Changes from baseline suggested beneficial effects in selected patients, e.g. improvement in 6MWD (+31m), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels (-347 pg/mL) and WHO FC I/II/III/IV,% (2/52/46/0), cardiac index (+0.3 L/min/m²).

Soluble Guanylate Cyclase Stimulators

Concomitant use of riociguat 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 coumarin-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

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

Inhibitors for the UDP-Glykosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: 1/10th to 1/3rd of riociguat). For co-administration with these substances follow the recommendation on dose titration (see section 4.2).

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-treatment of medicinal products 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). For co-administration with bosentan follow the recommendation on dose titration (see section 4.2).

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. For co-administration with strong CYP3A4 inducers follow the recommendation on dose titration (see section 4.2).

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 strong inhibitors of CYP1A1 *in vitro*. Therefore, clinically relevant drug-drug interactions with co-treatment which are significantly cleared by CYP1A1-mediated biotransformation, such as erlotinib or granisetron cannot be ruled out.

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.

Patients must not get pregnant during Adempas therapy (see section 4.3). Riociguat (2.5 mg three times per day) did not have a clinically meaningful effect on the plasma levels of combined oral contraceptives containing levonorgestrel and ethinyl estradiol when concomitantly administered to healthy female subjects. Based on this study and as riociguat is not an inducer of any of the relevant metabolic enzymes, also no pharmacokinetic interaction is expected with other hormonal contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

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

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.

Breast-feeding

No data on the use of riociguat in breast-feeding women are available. Data from animals indicate that riociguat is excreted into milk. Due to the potential for serious adverse reactions in breast-fed 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 medicinal product.

Fertility

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

4.7 Effects on ability to drive and use machines

Adempas has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to this medicinal product, before driving or using 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). With longer observation in uncontrolled long term extension studies the safety profile was similar to that observed in the placebo controlled phase III trials.

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 $\geq 10\%$ 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

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

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

In case of overdose, standard supportive measures should be adopted as required. In case of pronounced hypotension, active cardiovascular support may be required. Based on the high plasma protein binding riociguat is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives (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

Adverse Events leading to discontinuation occurred at a similar frequency in both treatment groups (riociguat individual dose titration (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 from 15 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

Treatment duration in CHEST-2	Changes in WHO Functional Class (n (%) of patients)		
	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 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·s·cm ⁻⁵) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline (dyn·s·cm ⁻⁵) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference (dyn·s·cm ⁻⁵) 95% CI, [p-value]	-225.7 -281.4 to -170.1 [<0.0001]		
NT-proBNP	Riociguat IDT (n = 228)	Placebo (n = 106)	Riociguat CT (n=54)
Baseline (ng/L) [SD]	1,026.7 [1,799.2]	1,228.1 [1,774.9]	1,189.7 [1,404.7]
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

Treatment duration in PATENT-2	Changes in WHO Functional Class (n(%) of patients)		
	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.

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 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 4.3).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with riociguat in one or more subsets of the paediatric population in the treatment of pulmonary hypertension.

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of riociguat is high (94%). Riociguat is rapidly absorbed with maximum concentrations (C_{max}) appearing 1-1.5 hours after tablet intake. Intake with food reduced riociguat AUC slightly, C_{max} was reduced by 35%.

Bioavailability (AUC and C_{max}) is comparable for riociguat administered orally as a crushed tablet suspended in apple sauce 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.

Biotransformation

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 (type B)
hypromellose 5 cP
magnesium stearate
lactose monohydrate
sodium laurilsulfate

Film-coat:

hydroxypropylcellulose
hypromellose 3 cP
propylene glycol (E 1520)
titanium dioxide (E 171)
iron oxide yellow (E 172) (in 1 mg, 1.5 mg, 2 mg and 2.5 mg tablets only)
iron oxide red (E 172) (in 2 mg and 2.5 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blister.

Pack sizes: 42, 84, 90 or 294 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Adempas 0.5 mg film-coated tablets

EU/1/13/907/001

EU/1/13/907/002

EU/1/13/907/003

EU/1/13/907/016

Adempas 1 mg film-coated tablets

EU/1/13/907/004

EU/1/13/907/005

EU/1/13/907/006

EU/1/13/907/017

Adempas 1.5 mg film-coated tablets

EU/1/13/907/007

EU/1/13/907/008

EU/1/13/907/009

EU/1/13/907/018

Adempas 2 mg film-coated tablets

EU/1/13/907/010

EU/1/13/907/011

EU/1/13/907/012

EU/1/13/907/019

Adempas 2.5 mg film-coated tablets

EU/1/13/907/013

EU/1/13/907/014

EU/1/13/907/015

EU/1/13/907/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 March 2014

Date of latest renewal: 18 January 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

Bayer (logo)

12. MARKETING AUTHORISATION NUMBER

Adempas 0.5 mg – pack of 42 film-coated tablets - EU/1/13/907/001
Adempas 0.5 mg – pack of 84 film-coated tablets - EU/1/13/907/002
Adempas 0.5 mg – pack of 90 film-coated tablets - EU/1/13/907/003
Adempas 0.5 mg – pack of 294 film-coated tablets - EU/1/13/907/016
Adempas 1 mg – pack of 42 film-coated tablets - EU/1/13/907/004
Adempas 1 mg – pack of 84 film-coated tablets - EU/1/13/907/005
Adempas 1 mg – pack of 90 film-coated tablets - EU/1/13/907/006
Adempas 1 mg – pack of 294 film-coated tablets - EU/1/13/907/017
Adempas 1.5 mg – pack of 42 film-coated tablets - EU/1/13/907/007
Adempas 1.5 mg – pack of 84 film-coated tablets - EU/1/13/907/008
Adempas 1.5 mg – pack of 90 film-coated tablets - EU/1/13/907/009
Adempas 1.5 mg – pack of 294 film-coated tablets - EU/1/13/907/018
Adempas 2 mg – pack of 42 film-coated tablets - EU/1/13/907/010
Adempas 2 mg – pack of 84 film-coated tablets - EU/1/13/907/011
Adempas 2 mg – pack of 90 film-coated tablets - EU/1/13/907/012
Adempas 2 mg – pack of 294 film-coated tablets - EU/1/13/907/019
Adempas 2.5 mg – pack of 42 film-coated tablets - EU/1/13/907/013
Adempas 2.5 mg – pack of 84 film-coated tablets - EU/1/13/907/014
Adempas 2.5 mg – pack of 90 film-coated tablets - EU/1/13/907/015
Adempas 2.5 mg – pack of 294 film-coated tablets - EU/1/13/907/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER - PACKS OF 42, 84, 90, 294 FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.5 mg tablets
Adempas 1 mg tablets
Adempas 1.5 mg tablets
Adempas 2 mg tablets
Adempas 2.5 mg tablets
riociguat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN



B. PACKAGE LEAFLET

Package Leaflet: Information for the user

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

riociguat

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

1. What Adempas is and what it is used for
2. What you need to know before you take Adempas
3. How to take Adempas
4. Possible side effects
5. How to store Adempas
6. Contents of the pack and other information

1. What Adempas is and what it is used for

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

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

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

2. What you need to know before you take Adempas

Do not take Adempas:

- if you are taking certain medicines called **PDE5 inhibitors** (e.g. sildenafil, tadalafil, vardenafil). These are medicines used for the treatment of high blood pressure in the arteries of the lungs (PAH) or erectile dysfunction.
- if you have **severe liver problems** (severe hepatic impairment, Child Pugh C).
- if you are **allergic** to riociguat or any of the other ingredients of this medicine (listed in section 6).
- if you are **pregnant**.
- if you are taking **nitrates** or **nitric oxide donors** (such as amyl nitrite) in any form, medicines often used to treat high blood pressure, chest pain or heart disease. This also includes recreational drugs called poppers.
- if you are taking other **soluble guanylate cyclase stimulators**. Ask your doctor if you are not sure if you are taking a soluble guanylate cyclase stimulator.
- if you have **low blood pressure** (systolic blood pressure less than 95 mmHg) before starting first treatment with this medicine.
- if you have increased pressure in your pulmonary circulation associated with scarring of the lungs, of unknown cause (idiopathic pulmonary pneumonia).

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

Warnings and precautions

Talk to your doctor or pharmacist before taking Adempas if:

- you have recently experienced serious **bleeding from the lung**, or if you have undergone treatment to stop **coughing up blood** (bronchial arterial embolisation).
- you take **blood-thinning medicines** (anticoagulants) since this may cause bleeding from the lungs. Your doctor will regularly monitor you.
- you feel **short of breath** during treatment with this medicine, this can be caused by a build-up of fluid in the lungs. Talk to your doctor if this happens.
- you have any symptoms of **low blood pressure** (hypotension) such as dizziness, lightheadedness, or fainting or if you are taking medicines to lower your blood pressure or medicines that cause an increase in urination or if you have problems with your heart or circulation. Your doctor may decide to monitor your blood pressure. If you are older than 65 years, you have an increased risk of developing low blood pressure.
- you take medicines used to **treat fungal infections** (e.g. ketoconazole, posaconazole, itraconazole) or medicines for the **treatment of HIV infection** (e.g. abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir). Your doctor will monitor your health status and should consider a reduced starting dose for Adempas.
- your **kidneys do not work properly** (creatinine clearance < 30 ml/min) or if you are **on dialysis** as the use of this medicine is not recommended.
- you have **moderate liver problems** (hepatic impairment, Child Pugh B).
- you start or stop **smoking** during treatment with this medicine, because this may influence the level of riociguat in your blood.

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

Children and adolescents

The use of Adempas in children and adolescents (under 18 years of age) should be avoided because efficacy and safety have not been established for this age group.

Other medicines and Adempas

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, in particular, medicines used for:

- high blood pressure or heart disease (such as nitrates and amyl nitrite in any form or other soluble guanylate cyclase stimulators), as you must not take those medicines together with Adempas.
- high blood pressure in the lung vessels (the pulmonary arteries), as you must not take certain medicines (sildenafil and tadalafil) together with Adempas. Other medicines for high blood pressure in the lung vessels (PAH), such as bosentan and iloprost, can be used with Adempas, but you should still tell your doctor.
- erectile dysfunction (such as sildenafil, tadalafil, vardenafil), as you must not take those medicines together with Adempas.
- fungal infections (such as ketoconazole, posaconazole, itraconazole) or HIV infection (such as abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, rilpivirine or ritonavir) because alternative treatment options may be considered. If you already take one of these medicines and start treatment with Adempas, your doctor will monitor your health status and should consider a reduced starting dose for Adempas.
- epilepsy (e.g. phenytoin, carbamazepine, phenobarbitone).
- depression (St. John's Wort).
- preventing rejection of transplanted organs (ciclosporin).
- joint and muscular pain (niflumic acid).
- cancer (such as erlotinib, gefitinib).
- stomach disease or heartburn (antacids such as aluminium hydroxide/magnesium hydroxide). These antacid medicines should be taken at least two hours before or one hour after taking Adempas.
- nausea, vomiting (feeling or being sick) (such as granisetron).

Smoking

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

Pregnancy and breast-feeding

Pregnancy

Do not take Adempas during pregnancy. If there is a chance you could become pregnant, use reliable forms of contraception while you are taking these tablets. You are also advised to take monthly pregnancy tests. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding

If you are breast-feeding or planning to breast-feed, ask your doctor or pharmacist for advice before taking this medicine because it might harm your baby. You should not breast-feed while taking this medicine. Your doctor will decide with you if you either should stop breast-feeding or stop treatment with Adempas.

Driving and using machines

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

Adempas contains lactose

If you have been told by a doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Adempas contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”.

3. How to take Adempas

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

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

Crushed tablets:

If you have difficulty swallowing the whole tablet, talk to your doctor about other ways to take Adempas. The tablet may be crushed and mixed with water or a soft food, such as apple sauce, immediately before you take it.

Dose

The recommended starting dose is a 1-mg tablet taken 3 times a day for 2 weeks.

The tablets should be taken 3 times a day, approximately 6 to 8 hours apart. They can generally be taken with or without food.

However, if you are prone to having low blood pressure (hypotension), you should not switch from taking Adempas with food to taking Adempas without food because it may affect how you react to this medicine.

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

Special considerations for patients with kidney or liver problems

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

65 years or older

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

Special considerations for patients who smoke

You should tell your doctor if you start or stop smoking during treatment with this medicine. Your dose may be adjusted.

If you take more Adempas than you should

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

If you forget to take Adempas

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

If you stop taking Adempas

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

If you are transitioning between sildenafil or tadalafil and Adempas

- If you are stopping sildenafil, you must wait at least 24 hours before you take Adempas.
- If you are stopping tadalafil, you must wait at least 48 hours before you take Adempas.
- If you are stopping Adempas to change to another medicine called a PDE5 inhibitor (e.g. sildenafil or tadalafil) you must wait at least 24 hours from your last dose of Adempas before you take the PDE5 inhibitor.

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

4. Possible side effects

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

The most **serious** side effects are:

- **coughing up blood** (haemoptysis) (common side effect, may affect up to 1 in 10 people),
- **acute bleeding from the lungs** (pulmonary haemorrhage) may result in coughing up blood, cases with fatal outcomes were observed (uncommon side effect, may affect up to 1 in 100 people).

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

Overall list of possible side effects:

Very common: may affect more than 1 in 10 people

- headache
- dizziness
- indigestion (dyspepsia)
- swelling of limbs (oedema peripheral)
- diarrhoea
- feeling or being sick (nausea and vomiting)

Common: may affect up to 1 in 10 people

- inflammation of the stomach (gastritis)
- inflammation in the digestive system (gastroenteritis)
- reduction of red blood cells (anaemia) seen as pale skin, weakness or breathlessness
- awareness of an irregular, hard, or rapid heartbeat (palpitation)
- low blood pressure (hypotension)
- nose bleed (epistaxis)
- difficulty breathing through your nose (nasal congestion)
- pain in the stomach, intestine or abdomen (gastrointestinal and abdominal pain)
- heartburn (gastro-oesophageal reflux disease)
- difficulty in swallowing (dysphagia)
- constipation
- bloating (abdominal distension)

Reporting of side effects

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

5. How to store Adempas

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

This medicine does not require any special storage conditions.

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

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

6. Contents of the pack and other information

What Adempas contains

- The **active substance** is riociguat.
 - Adempas 0.5 mg film-coated tablets*
Each film-coated tablet contains 0.5 mg riociguat.
 - Adempas 1 mg film-coated tablets*
Each film-coated tablet contains 1 mg riociguat.
 - Adempas 1.5 mg film-coated tablets*
Each film-coated tablet contains 1.5 mg riociguat.
 - Adempas 2 mg film-coated tablets*
Each film-coated tablet contains 2 mg riociguat.
 - Adempas 2.5 mg film-coated tablets*
Each film-coated tablet contains 2.5 mg riociguat.

- The **other ingredients** are:
 - Tablet core:* cellulose microcrystalline, crospovidone (type B), hypromellose 5 cP, lactose monohydrate, magnesium stearate and sodium laurilsulfate (see end of section 2 for further information on lactose).
 - Film-coat:* hydroxypropylcellulose, hypromellose 3 cP, propylene glycol (E 1520) and titanium dioxide (E 171).
 - Adempas 1 mg, 1.5 mg tablets also contains iron oxide yellow (E 172).
 - Adempas 2 mg and 2.5 mg tablets also contains iron oxide yellow (E172) and iron oxide red (E 172).

What Adempas looks like and contents of the pack

Adempas is a film-coated tablet:

Adempas 0.5 mg film-coated tablets

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

Adempas 1 mg film-coated tablets

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

Adempas 1.5 mg film-coated tablets

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

Adempas 2 mg film-coated tablets

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

Adempas 2.5 mg film-coated tablets

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

They are available in packs of:

- 42 tablets: two transparent calendar blisters of 21 tablets each.
- 84 tablets: four transparent calendar blisters of 21 tablets each.
- 90 tablets: five transparent blisters of 18 tablets each.
- 294 tablets: fourteen transparent calendar blisters of 21 tablets each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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