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)

Adults
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 (see section 5.1).

Paediatrics
Adempas is indicated for the treatment of PAH in paediatric patients aged 6 to less than 18 years with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists (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

Starting dose
The recommended starting dose is 1 mg 3 times daily for 2 weeks. Tablets should be taken 3 times daily approximately 6 to 8 hours apart (see section 5.2).

Titration

Adult patients
Dose should be increased in 2-week intervals by 0.5 mg 3 times daily to a maximum of 2.5 mg 3 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 3 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 3 times daily.

Paediatric PAH patients aged 6 to < 18 years with body weight ≥ 50 kg
Adempas is available for paediatric use as a tablet for those with body weight ≥ 50 kg.
Titration of riociguat dose is to be performed based on the patient's systolic blood pressure and general tolerability at the discretion of the treating physician/healthcare provider. If the patient has no signs or symptoms of hypotension and systolic blood pressure is ≥ 90 mmHg for the 6 to < 12 year age

group or ≥ 95 mmHg for the 12 to < 18 year age group, the dose should be increased in 2-week intervals by 0.5 mg 3 times daily to a maximum daily dose of 3 times 2.5 mg.
If systolic blood pressure falls below these specified levels the dosage should be maintained as long as 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 the specified levels, and the patient shows signs or symptoms of hypotension the current dose should be decreased by 0.5 mg 3 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) for adults and paediatric patients with body weight of at least 50 kg.
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.

Paediatric PAH patients weighing less than 50 kg
Adempas is available as granules for oral suspension to treat paediatric PAH patients at least 6 years of age and weighing less than 50 kg – see Summary of Product Characteristics for Adempas granules for oral suspension for further direction. Patients may switch between tablets and oral suspension during therapy due to body weight changes.

Treatment discontinuation
In case treatment has to be interrupted for 3 days or more, treatment should be restarted with 1 mg 3 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 in adults and children at least 24 hours prior to administration of riociguat.
Tadalafil must be discontinued at least 48 hours in adults and 72 hours in children prior to administration of riociguat.
Riociguat must be discontinued in adults and children 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 riociguat 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.
No clinical data are available in children and adolescents less than 18 years of age with hepatic impairment.

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 riociguat 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.
No clinical data are available in children and adolescents less than 18 years of age with renal impairment.

Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors
Coadministration of riociguat with strong multi pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to riociguat (see section 4.5 When initiating riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of 0.5 mg 3 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 riociguat doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see section 4.5).
No clinical data are available in children and adolescents less than 18 years of age receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors.

Paediatric population
The safety and efficacy of riociguat have not been established in the following paediatric populations:
- Children aged < 6 years (see section 4.1), because of safety concerns. Non clinical data show undesirable effects on growing bone (see section 5.3).
- Children with PAH aged 6 to < 12 years with systolic blood pressure < 90 mmHg at treatment initiation (see section 4.3)
- Children and adolescents with PAH aged 12 to < 18 years with systolic blood pressure <95 mmHg at treatment initiation (see section 4.3)
- Children and adolescents with CTEPH aged < 18 years old (see section 4.1).

No clinical trial data are available. Therefore, the use of riociguat is not recommended in these populations.

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 3 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.

<u>Method of administration</u>

For oral use.

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

Crushed tablets
For patients who are unable to swallow whole tablets, Adempas tablets may be crushed and mixed with water or soft foods 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.
- Treatment initiation for
  - children aged 6 to < 12 years with systolic blood pressure < 90 mmHg,
  - patients ≥ 12 years with systolic blood pressure < 95 mmHg.
- 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 adult 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 adult 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

Riociguat 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).

Excipients with known effect

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 medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have been performed only in adults. Therefore, the absolute extent of interactions in the paediatric population is not known. The interaction data obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of riociguat (2.5 mg tablets 3 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 riociguat 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 3 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 3 times daily) and riociguat (1.0 mg to 2.5 mg 3 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 reactions 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 (+31 m), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels (-347 pg/mL), percent distribution of WHO FC I/II/III/IV (2% / 52% / 46% / 0%), and cardiac index (+0.3 L/min/m^2).

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 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
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: 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. 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.
Assess the benefit-risk for each patient individually before prescribing riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors.
To mitigate the risk of hypotension when riociguat is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2).
In patients on stable doses of riociguat, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Concomitant use with CYP1A1, UGT1A1 and UGT1A9 inhibitors
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.
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). For co-administration with these substances follow the recommendation on dose titration (see section 4.2).

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 section 5.2).

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 riociguat therapy (see section 4.3). Riociguat (2.5 mg 3 times daily) 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 volunteers. 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 and female adolescents of childbearing potential must use effective contraception during treatment with riociguat.

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, riociguat 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 riociguat 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

Riociguat has moderate influence on the ability to cycle, 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 cycling, driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of riociguat in adults has been evaluated in phase III studies of 650 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 ≥ 10% of patients under riociguat treatment (up to 2.5 mg 3 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 riociguat (see section 4.4).

The safety profile of riociguat 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 riociguat 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), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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 riociguat in adult patients in phase III studies (pooled CHEST 1 and PATENT 1 data)

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

Paediatric patients

The safety of riociguat has been investigated in 24 paediatric patients aged 6 to less than 18 years over 24 weeks in an open-label uncontrolled trial (PATENT-CHILD) consisting of an individual dose titration phase starting with 1 mg (body weight adjusted) for 8 weeks and a maintenance phase for up

to 16 weeks (see section 4.2), followed by an optional long-term extension phase. Most common adverse reactions including the long-term extension phase were hypotension and headache occurring in 4/24, and 2/24 patients, respectively.

Overall, the safety data is consistent with the safety profile observed in adults.

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

In adults, 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 adult 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 3 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 reactions 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 adult 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 year (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 2 years and 89% after 3 years of riociguat treatment.

Efficacy in adult 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 3 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 3 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 reactions 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 adult 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 year (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.

Efficacy in paediatric patients with PAH

PATENT-CHILD

The safety and tolerability of riociguat 3 times daily for 24 weeks was evaluated in an open-label uncontrolled study in 24 paediatric patients with PAH aged 6 to less than 18 years (median 9.5 years). Only patients who were receiving stable doses of ERA (n=15, 62.5%) or ERA + prostacyclin analogue (PCA) (n=9, 37.5%) were enrolled, and they continued their PAH treatment during the study. The main exploratory efficacy endpoint of the study was exercise capacity (6MWD).

The aetiologies of PAH were idiopathic (n=18, 75.0%), persistent congenital PAH despite shunt closure (n=4, 16.7%), heritable (n=1, 4.2%), and pulmonary hypertension associated with developmental abnormalities (n=1, 4.2%). Two distinct age groups were included (≥ 6 to < 12 years [n=6] and ≥ 12 to < 18 years [n=18]).

At baseline, the majority of patients were WHO functional class II (n=18, 75%) one patient (4.2%) was WHO functional class I and five patients (20.8%) were WHO functional class III. The mean 6MWD at baseline was 442.12 m.

The 24-week treatment period was completed by 21 patients while 3 patients withdrew from the study due to adverse reactions.

For patients with assessments at baseline and at week 24:

- mean change in 6MWD from baseline +23.01 m (SD 68.8) (n=19)
- WHO functional class remained stable compared to baseline (n=21).
- median change in NT-proBNP was -12.05 pg/mL (n=14)

Two patients were hospitalised for right heart failure

Long-term data were generated from 21 patients who completed the first 24 weeks of treatment in PATENT-CHILD. All patients continued to receive riociguat in combination with either ERA or ERA

+ PCAs. The mean overall duration of exposure to riociguat treatment was 109.79 ± 80.38 weeks (up to 311.9 weeks), with 37.5% (n=9) of patients treated for at least 104 weeks and 8.3% (n=2) for at least 208 weeks.

During the long-term extension (LTE) phase improvements or stabilization in 6MWD were maintained for patients on treatment with observed mean changes from baseline (before start of treatment [PATENT-CHILD]) of +5.86 m at month 6, -3.43 m at month 12; +28.98 m at month 18 and -11.80 m at month 24.

A majority of patients remained stable regarding WHO functional class II between baseline and month 24. Clinical worsening was observed in 8 (33.3%) patients in total including the main phase. Hospitalization for right heart failure was reported in 5 (20.8%) patients. No deaths occurred during the observation period.

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 adult 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 reactions in patients treated with riociguat and a lack of efficacy. More patients taking riociguat died (11% vs. 4%) and had serious adverse reactions (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

Adults
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 water or in soft food compared to a whole tablet (see section 4.2).

Paediatric population
Children received riociguat tablet or oral suspension with or without food intake. Population PK modeling has shown that riociguat is readily absorbed in children as in adults, after oral administration as tablet or oral suspension. No difference in the absorption rate nor in the extent of absorption between the tablet and oral suspension formulation was observed.

Distribution

Adults
Plasma protein binding in adults 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.

Paediatric population
No data on riociguat plasma protein binding specific to children is available. Volume at steady-state (Vss) estimated via population pharmacokinetic modeling (age 6 to <18 years) following oral administration of riociguat is 26 L on average.

Biotransformation

Adults
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.

Paediatric population
No metabolism data specific to children and adolescents less than 18 years of age is available.

Elimination

Adults
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 volunteers and about 12 hours in patients.

Paediatric population
No mass balance study and metabolism data specific to children and adolescents less than 18 years of age are available. Clearance (CL) estimated via population PK modeling in children (age range 06 to < 18 years) following oral administration of riociguat is on average of 2.48 L/h. The geometric mean values for half-lives (t1/2) estimated via population PK modeling was 8.24 h.

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%.
The PK profile is similar in children as in adults.

Special populations

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

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
In adults pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
In adults pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

Hepatic impairment
In cirrhotic adult 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).
No clinical data is available in children and adolescents less than 18 years of age with hepatic impairment.

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 patients with renal impairment compared to patients with normal renal function. Corresponding values for the main metabolite were higher in patients with renal impairment compared to healthy volunteers. 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.
No clinical data is available in children and adolescents less than 18 years of age with renal impairment.

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 at doses 10 times the unbound AUC in the paediatric population. The clinical relevance of this finding is not known. No such effects were observed in juvenile rats at doses ≤ 2 times the unbound AUC in the paediatric population, or in adult rats. No new target organs were identified.

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 8-fold of human exposure (2.5 mg 3 times daily). In rabbits, starting at systemic exposure of about 4-fold of human exposure (2.5 mg 3 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
lactose monohydrate
magnesium stearate
sodium laurilsulfate

Tablet 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 https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.15 mg/mL granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with water, the oral suspension contains 0.15 mg riociguat per mL.

Excipient with known effect

Each mL of the oral suspension contains 1.8 mg sodium benzoate (E 211), (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension
White to off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adempas is indicated for the treatment of pulmonary arterial hypertension (PAH) in paediatric patients aged 6 to less than 18 years with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists (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 PAH. The child's weight and systolic blood pressure must be monitored, and the dose be checked regularly.

Posology

Paediatric PAH patients (aged 6 to less than 18 years, weighing less than 50 kg.)

Starting Dose
Patients will start with a body weight-adjusted riociguat dose given as oral suspension (see Table 1) to achieve systemic exposures equivalent to the starting dose in adults (1.0 mg 3 times daily). The oral suspension should be taken 3 times daily approximately 6 to 8 hours apart.

Titration

Titration scheme

Titration of riociguat dose is to be performed based on the patient's systolic blood pressure, at the discretion of the treating healthcare professional.

The dose should be increased by a body-weight adjusted equivalent to 0.5 mg 3 times daily for oral suspension in 2-week intervals to a maximum dose, a body-weight adjusted equivalent to 2.5 mg 3 times daily, if the patient has no signs or symptoms of hypotension and if systolic blood pressure is

- ≥ 90 mmHg for the 6 to < 12 year age group
- ≥ 95 mmHg for the 12 to < 18 year age group.

If systolic blood pressure falls below these specified levels, the dosage should be maintained as long as 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 the specified levels, and the patient shows signs or symptoms of hypotension, the current dose should be decreased stepwise by a body-weight adjusted equivalent to 0.5 mg 3 times daily.

Maintenance dose

The established individual dose should be maintained unless signs and symptoms of hypotension occur.
The maximum dose depends on the body weight and is shown in Table1.
If not tolerated, dose reduction should be considered at any time.

Table 1: Body weight-adjusted Adempas dosing for paediatric patients with a body weight less than 50 kg to achieve exposure equivalent to adults

Body weight (kg)	1.0 mg equivalent* (mL)	1.5 mg equivalent* (mL)	2.0 mg equivalent* (mL)	2.5 mg equivalent* (mL)
12 kg to < 14 kg	1.8	2.6	3.4	4.2
14 kg to <16 kg	1.8	2.8	3.8	4.6
16 kg to <18 kg	2.0	3.2	4.2	5.0
18 kg to <20 kg	2.2	3.4	4.4	5.5
20 kg to <25 kg	2.6	3.8	5.0	6.5
25 kg to <30 kg	3.0	4.4	6.0	7.5
30 kg to <35 kg	3.4	5.0	6.5	8.5
35 kg to <40 kg	3.8	5.5	7.5	9.5
40 kg to <50 kg	4.4	6.5	9.0	11.0

* single dose (mL) to be given 3 times daily

Missed dose

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

Treatment interruption

In case treatment has to be interrupted for 3 days or more, treatment should be restarted with a body weight adjusted equivalent to 1 mg 3 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 72 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).

PAH patients weighing 50 kg and more

Adempas is also available as a tablet to treat paediatric patients weighing 50 kg and more – see Summary of Product Characteristics for Adempas tablets for further direction. Patients may switch between tablets and oral suspension during therapy due to body weight changes.

Special populations

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

Hepatic impairment
Patients with severe hepatic impairment (Child Pugh C) have not been studied and therefore use of riociguat 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.
No clinical data are available in children and adolescents less than 18 years of age with hepatic impairment.

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 riociguat 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.
No clinical data are available in children and adolescents less than 18 years of age with renal impairment.

Patients on stable doses of strong multi pathway CYP / P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors
Coadministration of riociguat with strong multi pathway CYP and P-gp/BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) increases exposure to riociguat (see section 4.5). When initiating riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, consider a starting dose of a body weight adjusted equivalent to 0.5 mg of the oral suspension 3 times daily (see Table 2) 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 riociguat doses higher than or equal to a body weight adjusted equivalent to 1.0 mg of the oral suspension (see Table 2) if the patient develops signs or symptoms of hypotension (see section 4.5).
No clinical data are available in children and adolescents less than 18 years of age receiving concomitant systemic treatment with strong CYP/P-gp and BCRP inhibitors.

Table 2: Body weight-adjusted Adempas dose for paediatric patients with a body weight less than 50 kg to achieve exposure equivalent to 0.5 mg in adults

Body weight	12 kg to < 20 kg	20 kg to < 25 kg	25 kg to < 30 kg	30 kg to < 40 kg	40 kg to < 50 kg
0.5 mg equivalent (mL)*	1.0	1.2	1.4	1.8	2.2

* single dose (mL) to be given 3 times daily

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 a body-weight adjusted equivalent to2.5 mg 3 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.

Paediatric population
The safety and efficacy of riociguat have not been established in the following paediatric populations:
- Children aged < 6 years (see section 4.1), because of safety concerns. Non clinical data show undesirable effects on growing bone (see section 5.3).
- Children with PAH aged 6 to < 12 years with systolic blood pressure < 90 mmHg at treatment initiation (see section 4.3)
- Children and adolescents with PAH aged 12 to < 18 years with systolic blood pressure < 95 mmHg at treatment initiation (see section 4.3)
- Children and adolescents with Chronic thromboembolic pulmonary hypertension (CTEPH) aged < 18 years old (see section 4.1).

Method of administration

For oral use.

The healthcare professional should state the individual dose in ‘mL’ on the outer carton after ‘Dose:’.

To ensure accurate dosing, the healthcare professional should advise the patient or caregiver which blue syringe (Liquid Dosing Device Non-Luer) to use:

- Doses of up to 5 mL should be administered using the 5 mL syringe.
- Doses of more than 5 mL should be administered using the 10 mL syringe.
- Doses of 11 mL should be administered using the 10 mL syringe (2x 5.5 mL).

For instructions on reconstitution prior to administration, see section 6.6.

Patients, parents and/or caregivers should be instructed to read the ‘Instructions for Use’ carefully before using Adempas for the first time and before administering each dose. The patient must swallow the full dose of medicine.
Detailed ‘Instructions for Use’ are provided at the end of the package leaflet.

Food
Riociguat can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted riociguat intake are not recommended because of increased peak plasma levels of riociguat in the fasting compared to the fed state (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.
- Treatment initiation for
  - children aged 6 to < 12 years with systolic blood pressure < 90 mmHg,
  - patients ≥ 12 to < 18 years with systolic blood pressure < 95 mmHg.
- 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).

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).

Renal impairment

Data in adult 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).

Excipients with known effect

Adempas contains sodium benzoate
Granules for oral suspension contains 1.8 mg sodium benzoate (E 211) in each mL oral suspension.

Adempas contains sodium
Granules for oral suspension contain 0.5 mg sodium in each mL oral suspension. This medicinal product contains less than 1 mmol sodium (23 mg) per mL oral suspension, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have been performed only in adults. Therefore, the absolute extent of interactions in the paediatric population is not known. The interaction data obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Pharmacodynamic interactions

Nitrates
In a clinical study the highest dose of riociguat (2.5 mg tablets 3 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 riociguat 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 3 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 3 times daily) and riociguat (1.0 mg to 2.5 mg 3 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 reactions 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 (+31 m), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels (-347 pg/mL), percent distribution of WHO FC I/II/III/IV (2% / 52% / 46% / 0%), and cardiac index (+0.3 L/min/m^2).

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 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
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: 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. 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.
Assess the benefit-risk for each patient individually before prescribing riociguat in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors.
To mitigate the risk of hypotension when riociguat is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2).
In patients on stable doses of riociguat, the initiation of strong multi pathway CYP and P-gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

Concomitant use with CYP1A1, UGT1A1 and UGT1A9 inhibitors
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.
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). For co-administration with these substances follow the recommendation on dose titration (see section 4.2).

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 section 5.2).

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).

<u>Effects of riociguat on other substances</u>

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 riociguat therapy (see section 4.3). Riociguat (2.5 mg 3 times daily) 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 volunteers. 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 and female adolescent of childbearing potential must use effective contraception during treatment with riociguat.

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, riociguat 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 riociguat 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

Riociguat has moderate influence on the ability to cycle, 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 cycling, driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of riociguat in adults has been evaluated in phase III studies of 650 patients 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 ≥ 10% of patients under riociguat treatment (up to 2.5 mg 3 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 riociguat (see section 4.4).

The safety profile of riociguat 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 3).

Tabulated list of adverse reactions

The adverse reactions reported with riociguat 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), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 3: Adverse reactions reported with riociguat in adult patients in phase III studies (pooled CHEST 1 and PATENT 1 data)

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

Paediatric patients

The safety of riociguat has been investigated in 24 paediatric patients aged 6 to less than 18 years over 24 weeks in a open-label uncontrolled trial (PATENT-CHILD) consisting of an individual dose titration phase starting with 1 mg (body weight adjusted) for 8 weeks and a maintenance phase for up to 16 weeks (see section 4.2), followed by an optional long-term extension phase. Most common adverse reactions including the long-term extension phase were hypotension and headache occurring in 4/24, and 2/24 patients, respectively.

Overall, the safety data is consistent with the safety profile observed in adults.

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

In adults, 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 adult 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 3 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

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

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

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

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

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

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

PVR	**Riociguat IDT (n=232)**	**Placebo (n=107)**	**Riociguat CT (n=58)**
Baseline (dyn·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 6).

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

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

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

Adverse reactions 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 adult 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 7 shows the proportion of patients* with changes in WHO functional class during riociguat treatment compared to baseline.

Table 7: PATENT-2: Changes in WHO Functional Class

	Changes in WHO Functional Class (n(%) of patients)		
Treatment duration in PATENT-2	Improved	Stable	Worsened
1 year (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.

Efficacy in paediatric patients with PAH
PATENT-CHILD

The safety and tolerability of riociguat 3 times daily for 24 weeks was evaluated in an open-label uncontrolled study in 24 paediatric patients with PAH aged 6 to less than 18 years (median 9.5 years). Only patients who were receiving stable doses of ERA (n=15, 62.5%) or ERA + prostacyclin analogue (PCA) (n=9, 37.5%) were enrolled, and they continued their PAH treatment during the study. The main exploratory efficacy endpoint of the study was exercise capacity (6MWD).

The aetiologies of PAH were idiopathic (n=18, 75.0%), persistent congenital PAH despite shunt closure (n=4, 16.7%), heritable (n=1, 4.2%), and pulmonary hypertension associated with developmental abnormalities (n=1, 4.2%). Two distinct age groups were included (≥ 6 to < 12 years [n=6] and ≥ 12 to < 18 years [n=18]).

At baseline, the majority of patients were WHO functional class II (n=18, 75%) one patient (4.2%) was WHO functional class I and five patients (20.8%) were WHO functional class III. The mean 6MWD at baseline was 442.12 m.

The 24-week treatment period was completed by 21 patients while 3 patients withdrew from the study due to adverse reactions.

For patients with assessments at baseline and at week 24:
- mean change in 6MWD from baseline +23.01 m (SD 68.8) (n=19)
- WHO functional class remained stable compared to baseline (n=21).
- median change in NT-proBNP was -12.05 pg/mL (n=14)

Two patients were hospitalised for right heart failure.

Long-term data were generated from 21 patients who completed the first 24 weeks of treatment in PATENT-CHILD. All patients continued to receive riociguat in combination with either ERA or ERA + PCAs. The mean overall duration of exposure to riociguat treatment was 109.79 ± 80.38 weeks (up

to 311.9 weeks), with 37.5% (n=9) of patients treated for at least 104 weeks and 8.3% (n=2) for at least 208 weeks.

During the long-term extension (LTE) phase improvements or stabilization in 6MWD were maintained for patients on treatment with observed mean changes from baseline (before start of treatment [PATENT-CHILD]) of +5.86 m at month 6, -3.43 m at month 12; +28.98 m at month 18 and -11.80 m at month 24.

A majority of patients remained stable regarding WHO functional class II between baseline and month 24. Clinical worsening was observed in 8 (33.3%) patients in total including the main phase. Hospitalization for right heart failure was reported in 5 (20.8%) patients. No deaths occurred during the observation period.

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 adult 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 reactions in patients treated with riociguat and a lack of efficacy. More patients taking riociguat died (11% vs. 4%) and had serious adverse reactions (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

Adults
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 water or in soft food compared to a whole tablet (see section 4.2).

Paediatric population
Children received riociguat tablet or oral suspension with or without food intake. Population PK modeling has shown that riociguat is readily absorbed in children as in adults, after oral administration as tablet or oral suspension. No difference in the absorption rate nor in the extent of absorption between the tablet and oral suspension formulation was observed.

Distribution

Adults
Plasma protein binding in adults 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.

Paediatric population
No data on riociguat plasma protein binding specific to children is available. Volume at steady-state (Vss) estimated via population pharmacokinetic modeling in children (age range 6 to < 18 years) following oral administration of riociguat is 26 L on average.

Biotransformation

Adults
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.

Paediatric population
No metabolism data specific to children and adolescents less than 18 years of age is available.

Elimination

Adults
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 volunteers and about 12 hours in patients.

Paediatric population
No mass balance study and metabolism data specific to children and adolescents less than 18 years of age are available. Clearance (CL) estimated via population PK modeling in children (age range 6 to < 18 years) following oral administration of riociguat is on average of 2.48 L/h. The geometric mean values for half-lives (t1/2) estimated via population PK modeling was 8.24 h.

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%.
The PK profile is similar in children as in adults.

Special populations

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

Inter-ethnic differences
In adults pharmacokinetic data reveal no relevant inter-ethnic differences.

Different weight categories
In adults pharmacokinetic data reveal no relevant differences due to weight in the exposure to riociguat.

Hepatic impairment
In cirrhotic adult 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). No clinical data is available in children and adolescents less than 18 years of age with hepatic impairment.

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 patients with renal impairment compared to patients with normal renal function. Corresponding values for the main metabolite were higher in patients with renal impairment compared to healthy volunteers. 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.
No clinical data is available in children and adolescents less than 18 years of age with renal impairment.

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 at doses 10 times the unbound AUC in the paediatric population. The clinical relevance of this finding is not known. No such effects were observed in juvenile rats at doses ≤2 times the unbound AUC in the paediatric population, or in adult rats. No new target organs were identified.

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 8-fold of human exposure (2.5 mg 3 times daily). In rabbits, starting at systemic exposure of about 4-fold of human exposure (2.5 mg 3 times daily) abortion and foetal toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- anhydrous citric acid(E 330)
- flavour strawberry: consist of maltodextrin, propylene glycol (E 1520), triethyl citrate (E 1505), flavoring substances and flavoring preparations.
- hypromellose
- mannitol (E 421)
- microcrystalline cellulose and carmellose sodium
- sodium benzoate (E 211)
- sucralose (E 955)
- xanthan gum (E 415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution

After reconstitution the suspension is stable for 14 days at room temperature.
Store the reconstituted suspension upright.

6.4 Special precautions for storage

Do not store above 30 °C.
Do not freeze.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One carton contains:
- one 250 mL amber glass bottle (type III) with a child-resistant screw cap (polypropylene)
- one 100 mL water syringe (polypropylene)
- one bottle adapter (polypropylene/polyethylene/silicone)
- two 5 mL graduated blue syringes (polypropylene) for oral dosing
  The scale of the 5 mL blue syringe starts with 1 mL. The graduation marks are in increments of 0.2 mL.
- two 10 mL blue syringes syringes (polypropylene) for oral dosing
  The scale of the 10 mL blue syringe starts with 2 mL. The graduation marks are in increments of 0.5 mL.

6.6 Special precautions for disposal and other handling

Details on handling, preparation and administration of the oral suspension are given in the 'Instructions for Use' at the end of the package leaflet.

Instructions for reconsitution

Before preparation, the patient, parent and/or caregiver should thoroughly wash their hands with soap and dry them afterwards.

Before administration, the granules must be reconstituted with non-carbonated drinking water into a homogenous suspension. For details, see 'Instructions for Use' at the end of the package leaflet.

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)

EU/1/13/907/021

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 https://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

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

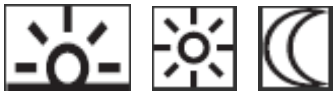
EXP

4. BATCH NUMBER

Lot

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN



PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR GLASS BOTTLE (GRANULES)

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.15 mg/mL granules for oral suspension
riociguat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 mL of oral suspension contains 0.15 mg riociguat.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension
The bottle contains 10.5 g granules or 208 mL after reconstitution.

1 water syringe 100 mL
2 blue syringes 5 mL
2 blue syringes 10 mL
1 bottle adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please ask your pharmacist or doctor to fill in the following data:
Dose: …….mL
3 times a day

For children below 50 kg

Shake during reconstitution for at least 60 seconds.
Shake before each use for at least 10 seconds.

Oral use only after reconstitution.
Read the package leaflet before 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

After reconstitution the suspension is stable for 14 days at room temperature.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C. Do not freeze. Store the prepared suspension upright.

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/021

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Adempas 0.15 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR GLASS BOTTLE (GRANULES)

1. NAME OF THE MEDICINAL PRODUCT

Adempas 0.15 mg/mL granules for oral suspension
riociguat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The bottle contains 10.5 g granules to be reconstituted in 200 mL of water. After reconstitution 1 mL of oral suspension contains 0.15 mg riociguat.

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension
The bottle contains 10.5 g granules or 208 mL after reconstitution.

1 water syringe 100 mL
2 blue syringes 5 mL
2 blue syringes 10 mL
1 bottle adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use only after reconstitution.
Read the package leaflet before use.

Shake during reconstitution for at least 60 seconds.
Shake before each use for at least 10 seconds.

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

Expiry date (reconstitution date + 14 days):

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C. Do not freeze. Store the prepared suspension upright.

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/907/021

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "the child" throughout.

What is in this leaflet

1. What Adempas is and what it is used for

Adempas contains the active substance riociguat, a guanylate cyclase (sGC)-stimulator.

It is used to treat adults and children from 6 years of age with certain types of pulmonary hypertension:
- **Chronic thromboembolic pulmonary hypertension (CTEPH)**.
  Adempas is used to treat adult patients with CTEPH. In patients with CTEPH, the blood vessels of the lung are blocked or narrowed by blood clots. The medicine can be used in patients with CTEPH who cannot be operated on, or in patients in whom pulmonary hypertension remains or returns after surgery.
- **Pulmonary arterial hypertension (PAH)**.
  Adempas is used to treat adults and children aged 6 years or older with pulmonary arterial hypertension. In these patients, the walls of the blood vessels of the lungs are thickened and the vessels become narrowed. In patients with PAH, Adempas is taken together with certain other medicines (so-called endothelin receptor antagonists). In adults, the medicine can also be taken on its own (monotherapy).

In patients with pulmonary hypertension, the blood vessels that carry blood from the heart to the lungs become narrowed, making it harder for the heart to pump blood to the lungs, 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. Adempas widens the blood vessels that lead from the heart to the lungs, reducing symptoms of the disease and better allowing patients to carry out physical activity better.

2. What you need to know before you take Adempas

Do not take Adempas if you
- take **PDE5 inhibitors** such as sildenafil, tadalafil, vardenafil. These are medicines to treat high blood pressure in lung arteries or erectile dysfunction.
- have **severely reduced liver function**.
- are **allergic** to riociguat or any of the other ingredients of this medicine (listed in section 6).
- are **pregnant.**
- take **nitrates** or **nitric oxide donors** such as amyl nitrite. These are medicines often used to treat high blood pressure, chest pain or heart disease. This also includes recreational drugs called poppers.
- take other medicines similar to Adempas called **soluble guanylate cyclase stimulators**, such as **vericiguat**. Ask your doctor if you are not sure.
- have **low blood pressure** before you take Adempas the first time. To start with Adempas your systolic blood value should be
  - 90 mmHg or more if your age is between 6 and 12 years,
  - 95 mmHg or more if you are 12 years old or older.
- have **increased blood pressure** in your lungs associated with scarring of the lungs, of unknown cause called idiopathic pulmonary pneumonia.

If any of these apply 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 **pulmonary veno-occlusive disease**, a disease which makes you **feel short of breath** because fluid builds-up in the lungs. He or she may decide to provide you with an alternative medicine.
- have recently had serious **bleeding from the lungs and airways**.
- have undergone treatment to stop **coughing up blood** (bronchial arterial embolisation).
- take medicines that prevent the blood from clotting since this may cause bleeding from the lungs. Your doctor will regularly test your blood and measure blood pressure.
- The doctor may decide to monitor the blood pressure, if you
  - have symptoms of **low blood pressure** like dizziness, lightheadedness or fainting, or
  - take medicines to lower blood pressure or to increase urination, or
  - have **heart or circulation problems**
  - are older than 65 years as low blood pressure is more likely in this age group.

Inform your doctor if
- you are **on dialysis** or if the **kidneys do not work properly**, as use of this medicine is not recommended.
- your **liver does not work properly**.

While using Adempas, talk to your doctor if you
- feel **short of breath** during treatment with this medicine. This can be caused by a build-up of fluid in the lungs. If this is due to pulmonary veno-occlusive disease your doctor may stop treatment with Adempas.
- start or stop **smoking** during treatment with this medicine, because this may influence the level of riociguat in your blood.

Children and adolescents
- **Chronic thromboembolic pulmonary hypertension (CTEPH)**
  - Adempas is not recommended for use in CTEPH patients less than 18 years of age.
- **Pulmonary arterial hypertension (PAH)**
  - You have been prescribed Adempas tablets. For PAH patients of 6 years and older that weigh less than 50 kg, Adempas is also available as granules for oral suspension. Patients may switch between tablets and oral suspension during therapy due to body weight changes**.**

    Efficacy and safety have not been shown in the following paediatric populations:

- Children less than 6 years because of safety concerns.

Other medicines and Adempas
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, in particular:
- **Do not take medicines used for**
  - high blood pressure or heart disease such as **nitrates** and **amyl nitrite**, or another **soluble guanylate cyclase stimulators** such as **vericiguat**. Do not take these medicines together with Adempas.
  - high blood pressure in lung arteries, as you must not take certain medicines such as **sildenafil, tadalafil** together with Adempas. Other medicines for high blood pressure in the lung arteries, such as **bosentan** and **iloprost**, can be used with Adempas, but you should inform the doctor.
  - erectile dysfunction such as **sildenafil, tadalafil, vardenafil**. Do not take these medicines together with Adempas.
- **The following medicines can increase the level of Adempas in the blood which increases the risk of side effects**
  - fungal infections such as **ketoconazole, posaconazole, itraconazole**.
  - HIV infection such as **abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, rilpivirine, ritonavir**.
  - epilepsy such as **phenytoin, carbamazepine, phenobarbitone**.
  - depression such as **St. John's Wort**.
  - preventing rejection of transplanted organs such as **ciclosporin**.
  - cancer such as **erlotinib, gefitinib**.
  - nausea, vomiting such as **granisetron**.
  - to treat stomach disease or heartburn called **antacids** such as **aluminium hydroxide / magnesium hydroxide** used. Take antacids at least 2 hours before or 1 hour after using Adempas.

Adempas with food
Adempas can generally be taken with or without food.
However, if your blood pressure tends to be low, take Adempas either always with food or always without food.

Pregnancy and breast-feeding
- **Birth control:** Women and female adolescents of childbearing potential must use effective contraception during treatment with Adempas. Talk to your doctor about suitable methods of contraception you may use to prevent pregnancy. In addition, you should take monthly pregnancy tests.
- **Pregnancy:** Do not use Adempas during pregnancy.
- **Breast-feeding:** Breast-feeding is not recommended while using this medicine because it might harm the baby. Inform your doctor if you are currently breast-feeding, or planning to breast-feed before using this medicine. Your doctor will decide with you to either stop breast-feeding or to stop using Adempas.

Driving and using machines
Adempas moderately influences the ability to cycle, drive and use machines. It may cause side effects such as dizziness. You should be aware of the side effects of this medicine before cycling, 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 tablet, 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.

Adempas is available as a tablet or granules for oral suspension.

Tablets are available for use by adults and children weighing at least 50 kg. Granules for oral suspension are available for children weighing less than 50 kg.

Treatment should only be started by a doctor experienced in the treatment of high blood pressure in lung arteries, who will monitor you during treatment. 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.

How to start treatment:
Your doctor will tell you what dose of Adempas to take.
- Treatment usually starts with a low dose.
- Your doctor will slowly increase your dose depending on how you respond to the treatment.
- During the first weeks of treatment the doctor will need to measure your blood pressure at least every two weeks. This is required to decide on the correct dose of your medicine.

How to take the medicine
Adempas is for oral use. The tablets should be taken 3 times a day, every 6 to 8 hours.

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 immediately before you take it.

How much you have to take
The recommended starting dose is a 1-mg tablet taken 3 times a day for 2 weeks.
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 very low blood pressure. In this case, your doctor will prescribe you Adempas at the highest dose you are comfortable on. The best dose will be selected by your doctor. For some patients' lower doses 3 times a day might be sufficient.

If you are 65 years or older
You may be at greater risk of low blood pressure. Your doctor may adjust the dose.

If you smoke
If you smoke, it is recommended that you stop before starting treatment, as smoking may reduce the effectiveness of these tablets. Please tell your doctor if you smoke or stop smoke during treatment. Your doctor may need to adjust your dose.

If you take more Adempas than you should
Please contact the doctor if you took more Adempas than you should and if you notice any side effects (see section 4). 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. If you stop to taking this medicine, your disease may worsen. If you have not taken this medicine for 3 days or more, please tell your doctor before you start taking it again.

If you are switching between Adempas and sildenafil or tadalafil
To avoid interactions, Adempas and PDE5 inhibitors (sildenafil, tadalafil) must not be taken at the same time.
- If you switch to Adempas
  - do not start Adempas for at least 24 hours after your last dose of sildenafil and at least 48 hours after your last dose of tadalafil.

- If you switch from Adempas
  - stop using Adempas at least 24 hours before you start using sildenafil or tadalafil.

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 **in adults** are:
- **coughing up blood** (haemoptysis) (common, may affect up to 1 in 10 people),
- **acute bleeding from the lungs** (pulmonary haemorrhage) which may result in coughing up blood and can be fatal (uncommon, 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 (in adult patients)

Very common: may affect more than 1 in 10 people
- dizziness
- headache
- indigestion (dyspepsia)
- diarrhoea
- feeling sick (nausea)
- vomiting
- swelling of limbs (oedema peripheral)

Common: may affect up to 1 in 10 people
- inflammation in the digestive system (gastroenteritis)
- low levels of red blood cells (anaemia). Symptoms are pale skin, weakness or breathlessness
- irregular, hard or rapid heartbeat (palpitations)
- low blood pressure (hypotension)
- nose bleed (epistaxis)
- difficulty breathing through your nose (nasal congestion)
- inflammation of the stomach (gastritis)
- heartburn (gastro-oesophageal reflux disease)
- difficulty in swallowing (dysphagia)
- pain in the stomach, intestine or abdomen (gastrointestinal and abdominal pain)
- constipation
- bloating (abdominal distension)

Side effects in children
In general, side effects observed in **children aged 6 to less than 18 years** treated with Adempas were similar to those observed in adults. The most **frequent** side effects **in children** were:
- **low blood pressure** (hypotension) (**Very common**: may affect more than 1 in 10 people)
- **headache** (**Common**: may affect up to 1 in 10 people)

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 and sodium).
  Tablet coat*:* hydroxypropylcellulose, hypromellose 3 cP, propylene glycol (E 1520) and titanium dioxide (E 171).
  Adempas 1 mg, 1.5 mg tablets also contain iron oxide yellow (E 172).
  Adempas 2 mg and 2.5 mg tablets also contain iron oxide yellow (E 172) and iron oxide red (E 172).

What Adempas looks like and contents of the pack
Adempas is a film-coated tablet (tablet):
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 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 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.

They are available in cartons of:
- 42 tablets: 2 transparent calendar blisters of 21 tablets each.
- 84 tablets: 4 transparent calendar blisters of 21 tablets each.
- 90 tablets: 5 transparent blisters of 18 tablets each.
- 294 tablets: 14 transparent calendar blisters of 21 tablets each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

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

Package leaflet: Information for the user

Adempas 0.15 mg/mL granules for oral suspension

riociguat

Read all of this leaflet carefully before you start using 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 the 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.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace "you" with "the child" throughout.

What is in this leaflet

1. What Adempas is and what it is used for

Adempas contains the active substance riociguat, a guanylate cyclase (sGC)-stimulator.

Pulmonary arterial hypertension (PAH).
Adempas is used to treat children from 6 years of age with pulmonary arterial hypertension. In these patients, the wall of the blood vessels of the lungs are thickened and therefore the vessels become narrowed. Adempas is taken together with certain other medicines (so-called endothelin receptor antagonists).

In patients with pulmonary hypertension, the blood vessels that carry blood from the heart to the lungs become narrowed, making it harder for the heart to pump blood to the lungs, 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. Adempas widens the blood vessels that lead from the heart to the lungs, reducing symptoms of the disease and better allowing patients to carry out physical activity better.

2. What you need to know before you use Adempas

Do not use Adempas if you
- use **PDE5 inhibitors** such as sildenafil, tadalafil, vardenafil. These are medicines to treat high blood pressure in lung arteries or erectile dysfunction.
- have **severely reduced liver function**.
- are **allergic** to riociguat or any of the other ingredients of this medicine (listed in section 6).
- are **pregnant.**
- use **nitrates** or **nitric oxide donors** such as amyl nitrite. These are medicines often used to treat high blood pressure, chest pain or heart disease. This also includes recreational drugs called poppers.
- use other medicines similar to Adempas called **soluble guanylate cyclases stimulators**, such as

vericiguat. Ask your doctor if you are not sure.
- have **low blood pressure** before you take Adempas the first time. To start with Adempas your systolic blood value should be
  - 90 mmHg or more if your age is between 6 and 12 years,
  - 95 mmHg or more if you are older than 12 and younger than 18 years.
- have **increased blood pressure** in your lungs associated with scarring of the lungs, of unknown cause called idiopathic pulmonary pneumonia.

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

Warnings and precautions
Talk to your doctor or pharmacist before using Adempas if you
- have **pulmonary veno-occlusive disease**, a disease which makes you **feel short of breath** because fluid builds-up in the lungs. He or she may decide to provide you with an alternative medicine.
- have recently had serious **bleeding from the lungs and airways**.
- have undergone treatment to stop **coughing up blood** (bronchial arterial embolisation).
- take medicines that prevent the blood from clotting since this may cause bleeding from the lungs. Your doctor will regularly test your blood and measure blood pressure.
- The doctor may decide to monitor the blood pressure, if you
  - have symptoms of **low blood pressure** like dizziness, lightheadedness or fainting, or
  - take medicines to lower blood pressure or to increase urination, or
  - have **heart or circulation problems**
- are older than 65 years as low blood pressure is more likely in this age group.

Inform your doctor if
- you are **on dialysis** or if the **kidneys do not work properly**, as use of this medicine is not recommended.
- your **liver does not work properly**.

While using Adempas, talk to your doctor if you
- feel **short of breath** during treatment with this medicine. This can be caused by a build-up of fluid in the lungs. If this is due to pulmonary veno-occlusive disease your doctor may stop treatment with Adempas.
- start or stop **smoking** during treatment with this medicine, because this may influence the level of riociguat in your blood.

Children and adolescents
Your have been prescribed Adempas granules for oral suspension. For PAH patients of 6 years and older that weigh 50 kg and more, Adempas is also available as tablets. Patients may be switched between granules for oral suspension and tablets during therapy due to body weight changes. Efficacy and safety have not been shown in the following paediatric populations:
- Children less than 6 years because of safety concerns.

Other medicines and Adempas
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, in particular:
- **Do not take medicines used for**
  - high blood pressure or heart disease such as **nitrates** and **amyl nitrite**, or another **soluble guanylate cyclase stimulators** such as **vericiguat**. Do not take these medicines together with Adempas.
  - high blood pressure in lung arteries, as you must not take certain medicines such as **sildenafil, tadalafil** together with Adempas. Other medicines for high blood pressure in the lung arteries, such as **bosentan** and **iloprost**, can be used with Adempas, but you should inform the doctor.
  - erectile dysfunction such as **sildenafil, tadalafil, vardenafil**. Do not take these medicines together with Adempas.

- **The following medicines can increase the level of Adempas in the blood which increases the risk of side effects. Medicines to treat**
  - fungal infections such as **ketoconazole, posaconazole, itraconazole.**
  - HIV infection such as **abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, rilpivirine, ritonavir**.
  - epilepsy such as **phenytoin, carbamazepine, phenobarbitone**.
  - depression such as **St. John's Wort**.
  - preventing rejection of transplanted organs such as **ciclosporin**.

  - cancer such as **erlotinib, gefitinib**.
  - nausea, vomiting such as **granisetron**.
  - stomach disease or heartburn called **antacids** such as **aluminium hydroxide / magnesium hydroxide**. Take antacids at least 2 hours before or 1 hour after using Adempas.

Adempas with food
Adempas can generally be taken with or without food.
However, if your blood pressure tends to be low, take Adempas either always with food or always without food.

Pregnancy and breast-feeding
- **Birth control:** Women and female adolescents of childbearing potential must use effective contraception during treatment with Adempas. Talk to your doctor about suitable methods of contraception you may use to prevent pregnancy. In addition, you should take monthly pregnancy tests.
- **Pregnancy:** Do not use Adempas during pregnancy.
- **Breast-feeding:** Breast-feeding is not recommended while using this medicine because it might harm the baby. Inform your doctor if you are currently breast-feeding, or planning to breast-feed before using this medicine. Your doctor will decide with you to either stop breast-feeding or to stop using Adempas.

Driving and using machines
Adempas moderately influences the ability to cycle, drive and use machines. It may cause side effects such as dizziness. You should be aware of the side effects of this medicine before cycling, driving or using any tools or machines (see section 4).

Adempas contains sodium benzoate
This medicine contains 1.8 mg sodium benzoate (E 211) in each mL oral suspension.

Adempas contains sodium
This medicine contains 0.5 mg sodium in each mL oral suspension. This medicine contains less than 1 mmol sodium (23 mg) per mL oral suspension, that is to say essentially "sodium-free".

3. How to use Adempas

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

Adempas is available as a tablet or granules for oral suspension.

Tablets are available for use by adults and children weighing at least 50 kg. Granules for oral suspension are available for children weighing less than 50 kg.

How to start treatment
Your doctor will tell you what dose of Adempas to take.
- Treatment usually starts with a low dose.

- Your doctor will slowly increase your dose depending on how you respond to the treatment.
- During the first weeks of treatment the doctor will need to measure your blood pressure at least every two weeks. This is required to decide on the correct dose of your medicine.

Your doctor will calculate and tell you the amount of oral suspension in millilitres (mL) you need to take. **Do not adjust the dose yourself.** The amount in mL needs to be measured with one of the blue syringes included in the Adempas carton. Your doctor or pharmacist will tell you which blue syringe to use (5 mL or 10 mL).

Before you use
- Make sure the correct dose is written on the carton. If not, ask your pharmacist or doctor to provide it. Keep the carton until the granules for oral suspension are used up.
- Follow the "Instructions for Use" included in the carton on how to prepare and use Adempas oral suspension carefully to avoid any handling problems e.g., clumps or sediment in the suspension.
- All materials to prepare and take the oral suspension are provided with the medicine. Only use non-sparkling water to avoid bubbles.

  Use only the syringes provided to administer Adempas to ensure correct dosing. Do not use any other method to take the suspension, such as alternative syringe, spoon etc.

How to take the medicine
Adempas is for oral use. Each Adempas dose has to be swallowed. The patient must swallow the full dose of medicine. Use Adempas 3 times daily, approximately every 6 to 8 hours.

How much you have to use
During the starting phase your doctor decides the dose of oral suspension every 2 weeks. The doctor will adjust the dose based on body weight and blood pressure. The maximum dose depends on the body weight. Your doctor will decide whether and when to switch between tablets and oral suspension during therapy due to body weight changes.

If you smoke
If you smoke, it is recommended that you stop before starting treatment, as smoking may reduce the effectiveness of this medicine. Please tell your doctor if you smoke or stop smoke during treatment. Your doctor may need to adjust your dose.

If you use more Adempas than you should
Please contact the doctor if you used more Adempas than you should and if you notice any side effects (see section 4). If the blood pressure drops (which can cause dizziness) then immediate medical attention may be needed.

If you forget to use Adempas
Do not use 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 using Adempas
Do not stop using this medicine without talking to your doctor first. If you stop to taking this medicine, your disease may worsen. If you have not taken this medicine for 3 days or more, please tell your doctor before you start taking it again.

If you are switching between Adempas and sildenafil or tadalafil
To avoid interactions, Adempas and PDE5 inhibitors (sildenafil, tadalafil) must not be taken at the same time.
- If you switch to Adempas
  - do not start Adempas for at least 24 hours after your last dose of sildenafil and at least 48 hours after your last dose of tadalafil.

- If you switch from Adempas
  - stop using Adempas at least 24 hours before you start using sildenafil or tadalafil.

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. Some of these may be serious. If this happens, **contact your doctor immediately** as you may need urgent medical treatment.

Side effects in children
In general, side effects observed in **children less than 18 years** treated with Adempas were similar to those observed in adults. The most **frequent** side effects **in children** were:
- **low blood pressure** (hypotension) (**Very common**: may affect more than 1 in 10 people)
- **headache** (**Common**: may affect up to 1 in 10 people)

Overall list of possible side effects (in adult patients)

Very common: may affect more than 1 in 10 people
- dizziness
- headache
- indigestion (dyspepsia)
- diarrhoea
- feeling sick (nausea)
- vomiting
- swelling of limbs (oedema peripheral)

Common: may affect up to 1 in 10 people
- inflammation in the digestive system (gastroenteritis)
- low levels of red blood cells (anaemia). Symptoms are pale skin, weakness or breathlessness
- irregular, hard or rapid heartbeat (palpitations)
- low blood pressure (hypotension)
- nose bleed (epistaxis)
- difficulty breathing through your nose (nasal congestion)
- inflammation of the stomach (gastritis)
- heartburn (gastro-oesophageal reflux disease)
- difficulty in swallowing (dysphagia)
- pain in the stomach, intestine or abdomen (gastrointestinal and abdominal pain)
- 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.

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

Do not store above 30 °C.
Do not freeze.

After reconstitution the shelf life of the suspension is 14 days at room temperature.

Store the prepared suspension upright.

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.
  After preparation, the oral suspension contains 10.5 g granules plus 200 mL water, which results in 208 mL suspension with 0.15 mg riociguat per mL.
- The other ingredients are anhydrous citric acid (E 330); flavour strawberry; hypromellose; mannitol (E 421); microcrystalline cellulose and carmellose sodium; sodium benzoate (E 211) (see end of section 2 for further information on sodium benzoate and sodium); sucralose (E 955); xanthan gum (E 415).

What Adempas looks like and contents of the pack
Adempas are white to off-white granules.
Content of the pack:
- 1 bottle (brown glass) containing 10.5 g Adempas granules, closed with a child-resistant screw cap.
- 1 water syringe 100 mL (for single use only) used to measure and add 200 mL of water to the bottle.
- 1 adapter for bottle and blue syringes.
- 2 blue syringes 5 mL with blue plunger to extract and orally administer Adempas (1 is a spare syringe). The scale of the 5 mL blue syringe starts with 1 mL. The graduation marks are in increments of 0.2 mL.
- 2 blue syringes 10 mL with blue plunger to extract and orally administer Adempas (1 is a spare syringe). The scale of the 10 mL blue syringe starts with 2 mL. The graduation marks are in increments of 0.5 mL.

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Manufacturer
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This leaflet was last revised in

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

Instructions for Use (IFU)

Adempas 0.15 mg/mL

250 mL bottle containing 10.5 g Adempas granules for preparation of oral suspension
Active ingredient: riociguat
Preparation and administration of the oral suspension (granules-water-mixture)

Before you start

- Adempas suspension is for oral use only.
- Your child's doctor will tell you the right dose volume and the frequency of administration.
  - **Always** use the volume prescribed by your child's doctor and have the correct dosing and frequency of administration written on the designated field on the outside of the box. Keep the box for the duration of use. If it is not written on the field, ask your child's doctor or pharmacist to provide the relevant information.
  - **Do not change the dose yourself.**
- Read all sections of the Instructions for Use carefully before using Adempas for the first time and before administering each dose.
- Be sure you understand the instructions before starting. If not, call your doctor or pharmacist.
- Keep the instructions for use so that you can refer to them later during the use of Adempas.
- Further information regarding Adempas can be found in the package leaflet.

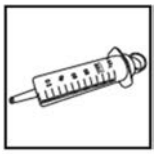
Cautionary information:

Do not unpack the single components until the instructions tell you to do so.
Do not use Adempas if any of the parts have been opened or are damaged.
Do not use Adempas after the expiry date which is stated on the box.
The box contains small parts. These can block the airways and lead to the risk of suffocation. **Keep out of the reach of babies and young children.**
Do not use the blue syringes for multiple patients as this can lead to infections.
Follow this "Instructions for Use" on how to prepare and use Adempas oral suspension and for **any question** contact your doctor, your pharmacist, or the local representative listed at the end of the Adempas package leaflet.

Packaging contents

Every box contains the following components:

1 bottle with child-resistant screw cap containing Adempas granules



1 packaged 100 mL water syringe (for single use only)

1 packaged bottle adapter

2 packaged 5 mL blue syringes (1 is a spare syringe)

2 packaged 10 mL blue syringes (1 is a spare syringe)

Using Adempas

- Adempas suspension is for oral use only.
- Your child's doctor will tell you the right dose volume and the frequency of administration.
  - **Always** use the volume prescribed by your child's doctor and have the correct dosing and frequency of administration written on the designated field on the outside of the box. Keep the box for the duration of use. If it is not written on the field, ask your child's doctor or pharmacist to provide the relevant information.
  - **Do not change the dose yourself.**
- Follow the detailed Instructions for Use given in the chapters below.
- Keep the instructions for use so that you can refer to them later during the use of Adempas.
- Take care to comply with the instructions concerning administration.

Preparing the oral suspension

Preparation – Get ready

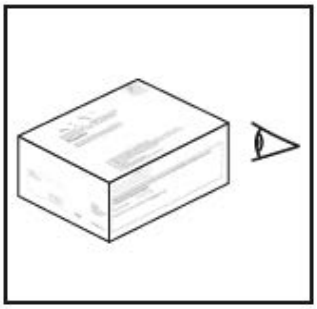
The preparation of the suspension is done once with every new box.
Before preparing the oral suspension:

a. Before you start, you will need the following equipment:
   - Get two containers (suchas a cup or bowl)
   - one container filled with drinking water,
   - The other container empty.

b. Obtain the following additional items:

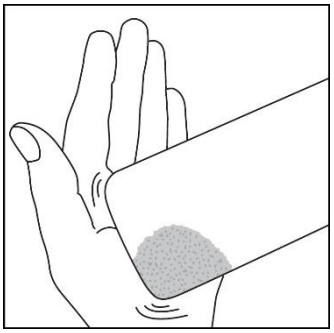
- Container with at least 300 mL of non-carbonated drinking water at room temperature
- Tissue for soaking up any excess water.

c. Thoroughly wash your hands with soap and dry them afterwards.



d. Check the expiry date on the box.
Do not use the medicine if the medicine has expired.

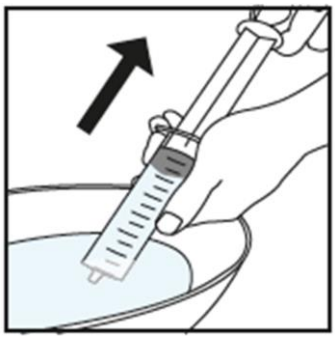
Adding 200 mL of water to the 250 mL bottle with granules



Every time you start a new box, use only the materials provided in the new box.

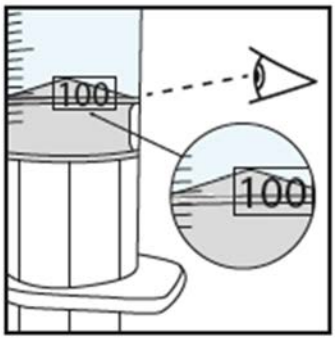
- Gently tap the bottle on your hand until granules flow freely.
- **Be careful** since the bottle is made of glass.

a. Unscrew the child-resistant cap of the bottle (push down and turn counter-clockwise).



b. Unpack the water syringe.
c. Dip the opening of the water syringe into the container with water.
d. Extract a volume of more than 100 mL.
e. To do this, pull up the plunger rod towards you, and make sure that the opening of the water syringe stays below the water surface all the time. This will avoid air bubbles in the syringe.
f. Take the syringe out of the water.

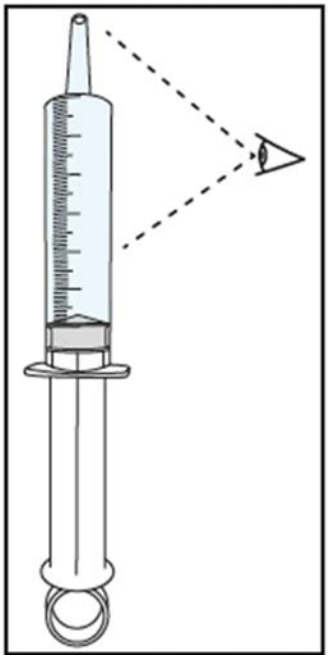
g. Turn the water syringe in a way that the opening is facing upwards.
→ Any air bubbles will move to the top when holding the syringe upwards.
Tap it with your fingers to further move any air bubble to the top.



h. Push the plunger rod until the upper ring of the plunger reaches the 100 mL mark.

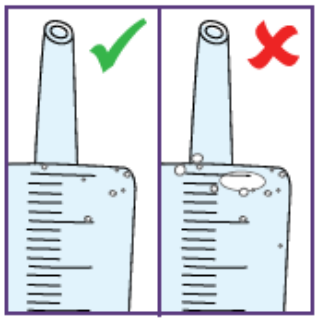
→ When pressing the plunger, water can come out of the tip of the water syringe. This wastewater can be soaked up with a tissue.

Cautionary information:
The upper ring of the black plunger **must be precisely in line with the 100 mL mark** to be able to achieve the correct concentration of the suspension.



i. Continue to hold the water syringe with the opening facing upwards and check the water in the syringe carefully:
   - for correct volume,
   - for air bubbles.

   Small air bubbles are not critical, but big air bubbles must be removed.



j. If the water syringe is not loaded correctly or contains too much air:
   a. Empty the water syringe
   b. Repeat steps c. to i.

k. Place the filled water syringe on the upper edge of the bottle opening.

l. Hold the bottle firmly.
Press the plunger rod down slowly.

The full volume of water must be transferred to the bottle.

m. **Repeat reconstitution steps (“c” to “l”) one more time.**

Cautionary information:

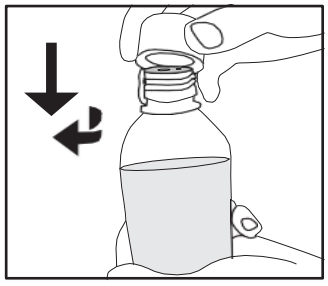
The bottle with granules to be filled in total with 200 mL of water (2 x 100 mL).

Fitting the adapter and mixing the oral suspension

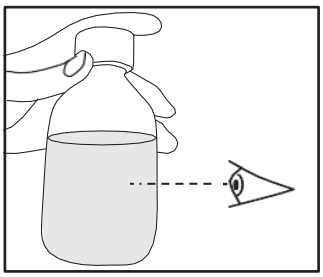
a. Unpack the bottle adapter.

b. Push the adapter **completely** into the neck of the bottle.

c. Close the bottle tightly with the screw cap.

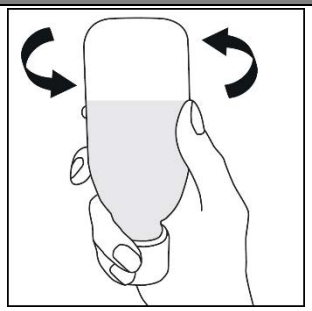


d. Shake the bottle **gently** for **at least 60 seconds**.
→ This is intended to provide a well-mixed suspension.



e. Check whether the suspension is thoroughly mixed:
- no clumps,
- no sediment.

Cautionary information:	For a correct dose: the suspension must **not** contain **any** clumps or sediment. Do not use the medicine as long as the suspension has clumps or sediment.



f.
If there are **clumps or sediment** → turn the bottle upside down
→ shake in different directions
→ if required, wait some time and shake again until no clumps or sediments are left .

Do not add more water to the bottle.

The suspension has a shelf life of 14 days at room temperature.

g. Write the date of expiry of the just prepared suspension on the label of the bottle
Expiry date (reconstitution date + 14 days)
The shown pictogram is only an example.

Setting the prescribed dose with every new blue syringe

Cautionary information:	**Once the dose has been fixed on the blue syringe, it cannot be changed.** ▪ **Do not remove the peelable label until you are prompted in the Instructions for Use.**

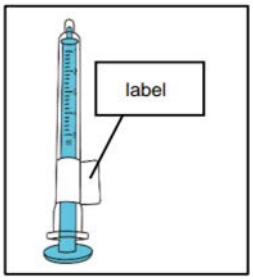
	▪ The blue syringe features a **red** button to adjust the volume. This button is initially covered by a peelable label. ▪ By pressing the **red** button the volume of the syringe is set, which can only be done once. ▪ **Do not** press the **red** button until the Instructions for Use tell you to do so.

Selecting a suitable blue syringe

Blue syringes with different volumes are included in this box:

- **5 mL blue syringes** for doses from **1 mL to 5 mL.**
- **10 mL blue syringes** for doses above **5 mL.**

In case the prescribed dose is 11 mL:
Use 2 x 5.5 mL with the 10 mL blue syringe.

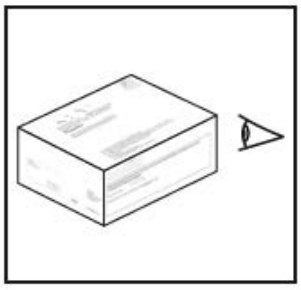


a. Select one suitable blue syringe based on the dose prescribed by your child's doctor.
b. Unpack the blue syringe.

Setting the required dose on new blue syringe

The blue syringe features a scale (mL).

- The scale of the 5 mL blue syringe starts with 1 mL. The graduation marks are in increments of 0.2 mL.
- The scale of the 10 mL blue syringe starts with 2 mL. The graduation marks are in increments of 0.5 mL.



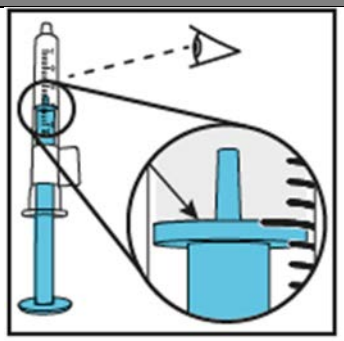
a. Review the dose provided in the respective field on the outside of the box.

b. If the information is not available:
Ask your doctor to provide it.

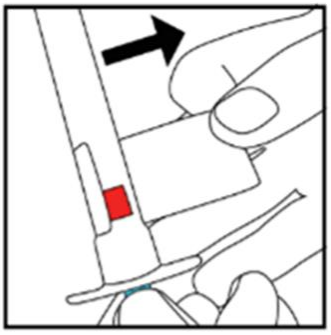
c. Hold the blue syringe with the opening pointing upwards.

d. Pull the plunger rod **slowly** until the upper margin reaches the mark of the volume to be administered.
When moving the plunger rod, you can hear a “Click” for each adjustable graduation mark.

Cautionary information:	The upper edge of the plunger **must be exactly in line** with the correct mark of the volume to be administered**.**



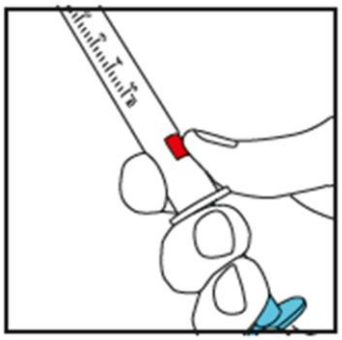
Be careful, do not pull the plunger past the volume to be administered.
Be careful, do not press on the label when pulling the plunger.



e. Remove the peelable label on the blue syringe **completely**.
You can now see the **red** button for setting the volume.

f. Check the position of the plunger again. Ensure the upper edge of the plunger is exactly in line with the correct mark of the volume to be administered.

g. If the position of the blue plunger does not match the required volume:
Adjust it accordingly.



h. If the position of the blue plunger matches the required volume, push the **red** button once to fix the adjustment.
→ Pressing the **red** button will produce a clicking sound.
→ The required dose is now set.

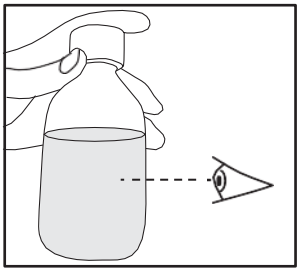
Cautionary information:	▪ If you notice that the wrong dose has been selected (the red button has been pushed) use the appropriate spare blue syringe. ▪ Repeat steps “a” to “h” with a new blue syringe.

i. Push the plunger upwards in the blue syringe as far as it goes. The blue syringe can now be used.

Administering the oral suspension

Shaking the oral suspension	Follow the steps described below for each required administration.
Cautionary information:	Allow the suspension to adjust to room temperature if it has been stored in the refrigerator.

a. **Gently** shake the bottle for **at least 10 seconds** before each dose. This is intended to provide a well-mixed suspension.



b. Check whether the suspension is mixed thoroughly, i.e.:
- no clumps,
- no sediment.

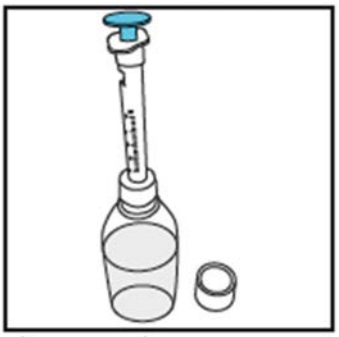
c. **If there are clumps or sediment:** Repeat former step "a"+"b".

Note	• Shaking can lead to formation of foam. • Let the bottle stand until the foam dissolves. • The larger opening visible on the adapter is used to connect the blue syringe. • The surface of the bottle adapter should be free of liquid.

d. Unscrew the bottle cap but keep the adapter on the top of the bottle.

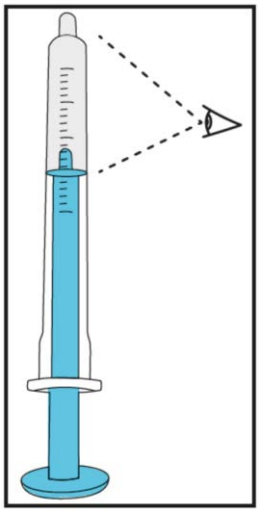
e. **If there is any liquid on the adapter:** Remove the liquid with a clean tissue.

Extracting the required dose



a. Keep the bottle in the upright position. Insert the tip of the blue syringe **fully** into the large opening of the adapter.

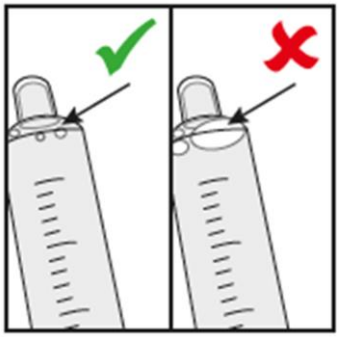
b. Turn the bottle upside down.
c. Pull up the blue plunger rod **slowly** until it stops (i.e. until the set dose is reached).



d. Carefully check for air in the blue syringe.
Smaller air bubbles are not critical.

e. If there are large air bubbles:
- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as possible.
- Repeat steps “b” to “e” above.

f. Return the bottle to the upright position.
g. Remove the blue syringe **carefully** from the adapter.

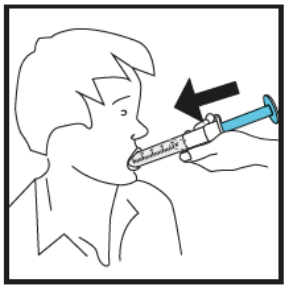


h. Hold the blue syringe upright and check whether:
→ the tip is filled,
→ the correct volume has been filled,
→ there are no large air bubbles.

i. If there are large air bubbles or air in the tip:
- Insert the tip of the blue syringe again fully into the large opening of the adapter.
- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as it goes.
- Repeat steps “b” to “h” until no large air bubbles are visible.

j. Close the bottle with the screw cap.
Administer the suspension immediately after filling the blue syringe.

Administration of prescribed dose



a. Place the blue syringe into the mouth of the patient.
b. Direct its tip into the cheek to allow for natural swallowing.
c. Push the plunger rod down **slowly** until the plunger stops (blue syringe is completely empty).
d. Ensure that the patient swallows the entire dose.

e. Encourage the patient to drink liquid afterwards.

Cautionary information:	▪ **The patient must swallow the full dose of medicine.**

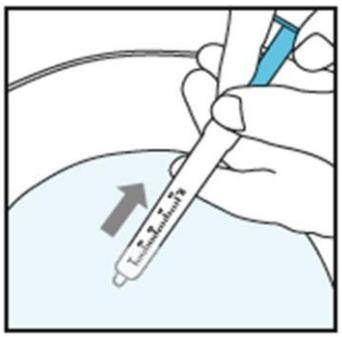
<u>Cleaning and storage</u>

The blue syringe must be cleaned following every application

Follow the steps listed below to clean the device. Altogether, **three** cycles of cleaning are necessary to ensure proper cleaning.

Cleaning

Cautionary information:	▪ Do not clean the blue syringe in the dish washer. ▪ Never boil the blue syringe.



a. Dip the tip of the blue syringe into the container of water.
b. Withdraw water until plunger rod stops.

c. Empty the blue syringe into the prepared empty container.

d. Repeat steps “a” to “c” **two more times**.
e. After cleaning, push the plunger rod back in until it stops.
f. Dry the outer surface of the syringe with a clean tissue.

Storage

Store the blue syringe in a clean and dry place until next use. Keep away from sunlight.

Disposal

Any unused medicine or waste material, syringes, and adapter should be disposed of in accordance with local requirements.