SUMMARY OF PRODUCT CHARACTERISTICS

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

- $\geq$ 90 mmHg for the 6 to < 12 year age group
- $\geq$ 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 Table 1.
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.

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

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 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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 ($dyn \cdot s \cdot cm^{-5}$) [SD]	791 [452.6]	834.1 [476.7]	847.8 [548.2]
Mean change from PVR baseline ($dyn \cdot s \cdot cm^{-5}$) [SD]	-223 [260.1]	-8.9 [316.6]	-167.8 [320.2]
Placebo-adjusted difference ($dyn \cdot s \cdot cm^{-5}$) 95% CI, [p-value]	-225.7 -281.4 to -170.1[<0.0001]		
NT-proBNP	**Riociguat IDT (n = 228)**	**Placebo (n = 106)**	**Riociguat CT (n=54)**
Baseline (ng/L) [SD]	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: $1/10^{th}$ to $1/3^{rd}$ 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 0.2mL.
- 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 0.5mL.

6.6 Special precautions for disposal

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 reconstitution

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 plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0756

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2025

10 DATE OF REVISION OF THE TEXT

19/09/2025