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Summary of the risk management plan (RMP) for Adempas (riociguat)

Overview of disease epidemiology

Pulmonary hypertension (PH) describes a condition of high blood pressure in the lungs. It is a long-term debilitating disorder. PH patients often experience symptoms such as shortness of breath, dizziness, fatigue and syncope (fainting), and the severity of symptoms usually worsens with the progression of the disease. In some situations, patients are bed-ridden. Sustained high pulmonary blood pressure in patients with PH frequently leads to heart failure and death.

Chronic thromboembolic pulmonary hypertension (CTEPH) affects mostly adults, and is a rare form of PH (3.2 cases per million adults according to a recent estimate). CTEPH is usually caused by blood clots in the lungs. In most patients who have a blood clot in the lungs, blood thinners are enough to restore blood flow to the lungs and prevent development of this form of PH. However, blood thinners do not work adequately for a minority of patients who may then develop CTEPH. The best and potentially curative treatment for 'operable' patients is pulmonary endarterectomy (PEA), a highly specialised surgical procedure. However, not all patients can be treated with PEA, and some patients who undergo PEA still have CTEPH after the surgery.

Pulmonary arterial hypertension (PAH) is another rare form of PH (15–52 cases per million people in European studies) that uniformly leads to death in both adults and children. PAH is characterised by structural changes (called 'vascular remodelling') to the arteries of the lungs. The arterial walls thicken, and the space inside the arteries is reduced. This causes restriction of blood flow and increased blood pressure in the lungs. Three classes of medicines that relax blood vessels are currently used to treat PAH: endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors and prostacyclin analogues. Despite treatment, most patients with PAH experience progression of their disease, and no cure has yet been found.

Summary of treatment benefits

CTEPH

The main clinical study of Adempas in patients with CTEPH is called CHEST-1. The duration of the study was 16 weeks, and 262 patients with CTEPH (who could not have surgery, or in whom CTEPH persisted or occurred again after surgery) took part. The patients were divided into two groups – one group received Adempas (1.0–2.5 mg three times daily) and the other group received placebo (a dummy treatment).

Adempas improved exercise capacity (measured as the distance patients were able to walk in six minutes) to a greater extent than placebo: after 16 weeks, patients treated with Adempas were able to walk further (on average 39 metres) in six minutes than they could when they started the study, compared with patients on placebo who walked (on average) 6 metres less in six minutes than they could at the start of the study.

PAH

The main clinical study of Adempas in patients with PAH is called PATENT-1. The duration of the study was 12 weeks, and 445 patients with PAH took part. The patients were divided into three groups: one group received Adempas at an individually titrated dose of 1.0–2.5 mg three times daily, one smaller group (63 patients) received Adempas titrated to a lower dose of 1.0-1.5 mg three times daily, and a third group received placebo. Adempas and placebo were used in combination with other PAH therapies (ERAs or prostacyclins) as required.

Adempas – taken with or without an ERA or prostacyclin analogue – improved exercise capacity to a greater extent than placebo: after 12 weeks, patients treated with Adempas were able to walk further (on average 30 metres) in six minutes than they could when they started the study, compared with patients on placebo who walked (on average) 6 metres less in six minutes than they were able to at the start of the study.

Unknowns relating to treatment benefits

CTEPH

In the studies, the majority of the patients were white and/or less than 65 years old. There is no evidence to suggest that results would be different in non-white patients or in older patients.

Adempas dose adjustment may be required for patients who smoke or start/stop smoking during treatment.

PAH

In the studies, the majority of the patients were white and/or less than 65 years old. There is no evidence to suggest that results would be different in non-white patients or in older patients.

Adempas dose adjustment may be required for patients who smoke or start/stop smoking during treatment.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypotension (low blood pressure)	In placebo-controlled clinical studies, approximately 10% of patients with CTEPH or PAH who received Adempas developed hypotension (low blood pressure); severe/serious cases were infrequent (0.2–0.4% of patients). Elderly patients (65 years or older) and patients with reduced kidney function may be at increased risk of developing hypotension.	During the first weeks of treatment with Adempas, blood pressure is measured to decide the correct dose of Adempas. Most hypotensive events occurred during the first Adempas dose titration in CHEST-1 and PATENT-1; once the appropriate dose had been identified for each patient, fewer events occurred during the rest of the study period.
	Use of Adempas in combination with nitrates or nitric oxide donors such as amyl nitrite (medicines use to treat high blood pressure or heart disease) may lead to hypotension (low blood pressure) and fainting. Patients	Co-administration of Adempas with nitrates or nitric oxide donors in any form is contraindicated.

Risk	What is known	Preventability
	receiving treatment with organic nitrates were excluded from the phase 3 clinical trials of Adempas in CTEPH and PAH (CHEST-1 and PATENT-1).	
	Use of Adempas in combination with a PDE-5 inhibitor (such as sildenafil, tadalafil or vardenafil) may lead to augmented blood-pressure-lowering effects and thus increase the risk of hypotension. Patients receiving treatment with PDE-5 inhibitors were excluded from the phase 3 clinical trials of Adempas in CTEPH and PAH.	Use of Adempas in combination with a PDE-5 inhibitor is contraindicated.
	Use of Adempas in combination with strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein/Breast Cancer Resistance Protein (P-gp/BCRP) inhibitors (such as ketoconazole [for fungal infections] or ritonavir [for HIV treatment]) results in increased levels of riociguat in the bloodstream.	Use of Adempas in combination with strong multi-pathway CYP and P-gp/BCRP inhibitors is not recommended.
	Use of Adempas in combination with a strong CYP1A1 inhibitor (such as erlotinib [for some types of cancer]) or a strong P-gp/BCRP inhibitor (such as cyclosporine A [used to prevent organ rejection after transplant]) may result in increased levels of riociguat in the bloodstream.	These medicinal products should be used with caution. Blood pressure should be monitored, and dose reduction of Adempas considered.
Upper gastrointestinal motility disorders	In clinical studies, upper gastrointestinal motility disorders such as dyspepsia (heartburn), gastro-oesophageal reflux disease (where stomach acid goes upwards into the oesophagus), dysphagia (difficulty swallowing) and gastritis (inflammation of the stomach) were common in patients receiving Adempas. Most were mild to moderate in severity.	Upper gastrointestinal motility disorders in patients receiving Adempas may be ameliorated by taking an antacid or a proton pump inhibitor – medications already approved for treatment of reflux disease.
Worsening of pulmonary venous occlusive disease (PVOD)	A special form of pulmonary hypertension (PVOD), not previously diagnosed in the patient, may be worsened by treatment with Adempas. This condition may cause fluid to build up in the lungs (pulmonary oedema) leading to shortness of breath, even weeks to months after the start of treatment with Adempas. In such cases, the treatment with Adempas must be stopped immediately.	Physicians should be alerted for signs of pulmonary oedema, and withdraw Adempas if a patient rapidly develops pulmonary oedema after starting treatment.
Serious haemoptysis/pulmonary haemorrhage (coughing up blood/bleeding from the lungs)	Bleeding from the lungs can occur as a result of the underlying disease in patients with CTEPH or PAH. Serious bleeding from the lungs – in a few cases with fatal outcome – was observed infrequently in patients with	Physicians should be aware of the risk of serious haemoptysis/pulmonary haemorrhage. Adempas use should be avoided in patients with recent serious

Risk	What is known	Preventability
	CTEPH or PAH receiving Adempas in clinical trials. Patients with recent serious bleeding from the lungs or patients who have undergone interventional treatment to stop bleeding from vessels in the lung (pulmonary arterial embolisation) might be at increased risk. In clinical trials in PAH and CTEPH, most patients were receiving treatment with a blood thinner. Blood thinners are part of PAH and CTEPH treatment recommendations. The general treatment recommendations for blood thinners (including optimal dosing) apply also to patients receiving Adempas.	bleeding from the lungs or patients who have undergone pulmonary arterial embolisation. Careful monitoring of patients taking blood thinners according to common medical practice is recommended. In case of bleeding from the lungs, the prescriber should regularly assess the benefits and risks of continuing treatment.

Important potential risks

Risk	What is known
Bleeding	In the phase 3 clinical trials CHEST-1 and PATENT-1, serious bleeding from sites other than the lungs was observed infrequently in patients with CTEPH or PAH who received Adempas. These serious bleeding events occurred in patients receiving blood thinners at the same time and were often associated with background medical conditions; overall, they were consistent with the expected rate of bleeding events in a population receiving blood thinners. However, no such events were observed in patients who received placebo. In clinical trials in PAH and CTEPH, most patients were receiving treatment with a blood thinner. Blood thinners are part of PAH and CTEPH treatment recommendations. The general treatment recommendations for blood thinners (including optimal dosing) apply also to patients receiving Adempas.
Embryo–fetal toxicity (potential defects in the unborn child)	In rats exposed to Adempas, heart defects in the developing fetus were observed. In rabbits exposed to Adempas, abortion and fetal toxicity were seen. There are no data on the use of Adempas in pregnant women. Therefore, Adempas is contraindicated during pregnancy, monthly pregnancy tests are recommended, and women of childbearing potential must use effective contraception during treatment with Adempas.
Medication error	Medication errors (e.g. overdose, accidental intake) were recorded in a small number of cases during the Adempas clinical trial programme. Adempas is a prescription only medicine, and treatment should be initiated and monitored by a physician experienced in the treatment of PAH or CTEPH. Patients are advised that they should always take Adempas exactly as their doctor has told them, and they should check with their doctor or pharmacist if they are not sure.
Renal failure	In the phase 3 clinical trials of Adempas in CTEPH and PAH (CHEST-1 and PATENT-1), kidney failure was reported more often in the Adempas group than in the placebo group, whereas clinical laboratory tests showed signs of worsening kidney function more often in the placebo group than in the Adempas group. Overall, events of reduced kidney function were very often associated with background medical conditions, including pre-existing medical history of reduced kidney function. Reduced kidney function may also occur as a result of progression of the underlying disease (worsening right heart failure) in patients with PAH. A specific signal for a potential negative impact of Adempas on kidney function could not be identified. Doctors need to establish carefully the appropriate dose of Adempas for patients with reduced kidney function.

Risk	What is known
Off-label use in patients aged < 18 years	The safety and efficacy of Adempas in children and adolescents below 18 years of age have not yet been established. No clinical data are available. Studies in rodents show an adverse effect on growing bone. Until more is known about the implications of these findings the use of Adempas in children and in growing adolescents should be avoided.
Treatment of patients with pre-existing atrial fibrillation (irregular heartbeat)	In the Adempas clinical trial programme, atrial fibrillation and atrial flutter (types of irregular heartbeat) were reported more often in patients receiving Adempas (1.7% and 0.8%, respectively) than in those receiving placebo (0% and 0.3%, respectively). However, this difference was not confirmed in the routine electrocardiogram (ECG) data (ECGs are tests to record the rhythm and electrical activity of the heart). Atrial fibrillation/flutter occurred more commonly in patients with a medical history of either condition than in patients without. In aggregate, the Adempas clinical trial data are consistent with the expected rate of atrial fibrillation/flutter in patients with pulmonary hypertension. Treatment to restore a normal heart rhythm is important to improve prognosis in patients with pulmonary hypertension and atrial fibrillation/flutter.
Bone changes and fractures	In the Adempas clinical trial programme, bone fractures occurred infrequently in patients with CTEPH or PAH who received placebo (0.3%) or Adempas (0.7%). The Adempas clinical trial data are consistent with the expected rate of bone fracture in severely ill patients.
Concomitant smoking (induction of CYP1A1)	In cigarette smokers, riociguat levels in the bloodstream are reduced by 50–60%. Therefore, patients are advised to stop smoking. Dose adjustment of Adempas may be required in patients who are smoking or who start or stop smoking during treatment.

Missing information

Risk	What is known
Patients with systolic blood pressure (blood pressure when the heart is contracting) < 95 mmHg at treatment initiation	Adempas treatment may lead to the development of hypotension (low blood pressure). The effect of Adempas in patients who already have low blood pressure before starting treatment is unknown. Adempas use is therefore contraindicated in patients with systolic blood pressure < 95 mmHg at treatment initiation.
Patients with severe liver problems (Child–Pugh C)	Impairment of liver function leads to increased levels of riociguat in the bloodstream. The effect of Adempas in patients with severe impairment of liver function (Child–Pugh C) has not been studied and therefore use of Adempas is contraindicated in these patients.
Patients with creatinine clearance < 30 mL/min or on dialysis (severe impairment of kidney function) or on dialysis	Impairment of kidney function leads to increased levels of riociguat in the bloodstream. Data in patients with creatinine clearance < 30 mL/min (i.e. with severely impaired kidney function) are limited and there are no data for patients on dialysis. Therefore, use of Adempas is not recommended in these patients.
Pregnancy and breastfeeding	There are no data on the use of Adempas in pregnant women. Studies in animals have shown reproductive toxicity (adverse effects in pregnancy) and placental transfer. Therefore, Adempas is contraindicated during pregnancy; monthly pregnancy tests are recommended, and women of childbearing potential must use effective contraception during treatment with Adempas. No data on the use of Adempas in breastfeeding women are available. Data from animals indicate that riociguat is secreted into milk. Due to the potential for serious adverse reactions in nursing infants, Adempas should not be used

Risk	What is known
	during breastfeeding. A risk to the suckling child cannot be excluded. Breastfeeding should be discontinued during treatment with this medicine.
Patients aged < 18 years	The safety and efficacy of Adempas in children and adolescents below 18 years of age have not yet been established. No clinical data are available. Studies in rodents show an adverse effect on growing bone. Until more is known about the implications of these findings the use of Adempas in children and in growing adolescents should be avoided.
Patients with CTEPH or PAH in WHO functional class IV (unable to carry out any physical activity without symptoms; breathlessness and/or fatigue may even be present at rest)	Patients in WHO functional class IV were not fully represented in the phase 3 clinical trials of Adempas (only those who were able to walk more than 150 m in 6 minutes at baseline were included).
Long-term safety in clinical practice	Long-term safety data are already available from patients taking Adempas for up to 5 years in clinical trials. However, further data will be collected by the marketing authorisation holder to confirm the long-term safety of Adempas outside of the controlled clinical trial setting.
Patients with uncontrolled hypertension (high blood pressure)	Uncontrolled high blood pressure is likely to be due to underlying disease of the heart/blood vessels and not directly associated with PAH and CTEPH. The effect of Adempas in patients who have uncontrolled high blood pressure is unknown.

Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Adempas can be found in the EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
EXPosur**E** Registry **R**iocigua**T** in patients with pulmonary	The main goal of this global registry is to monitor the safety of riociguat	**<u>Important identified risks:</u>** Hypotension • Including hypotension	Planned	Available data will be presented in PSUR/ PBRER

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
hypertension (EXPERT) (riociguat exposure registry)	in real life clinical use	due to drug interactions with: ○ organic nitrates ○ phosphodiesterase-5 inhibitors ○ strong multi-pathway CYP and P-gp/BCRP inhibitors ○ strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors Serious haemoptysis/ pulmonary haemorrhage **Important potential risks:** Bleeding Embryo–fetal toxicity Renal failure Off-label use in patients aged < 18 years Treatment of patients with pre-existing atrial fibrillation Bone changes and fractures Concomitant smoking (induction of CYP1A1) **Missing information:** Patients with systolic blood pressure < 95 mmHg at baseline Patients with severe hepatic impairment (Child–Pugh C) Patients with creatinine clearance < 30 mL/min or on dialysis Pregnancy and lactation Patients aged < 18 years Patients with CTEPH or PAH in WHO functional class IV Long-term safety in clinical practice Patients with uncontrolled hypertension		Final report estimated beginning 2019

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
In vitro studies to determine the substrate characteristics of riociguat and metabolite M-1 towards human transporters	To further define drug-drug interaction potential of riociguat and M-1	N/A	Ongoing/ initiated	Estimated December 2014
In vitro studies to determine the M-1 potential to inhibit renal efflux transporters MATE1 and MATE2K	To further define drug-drug interaction potential of riociguat and M-1	Unknown potential for drug-drug interactions	Ongoing	Estimated May 2014

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation (first application for marketing authorisation).

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 02-2014.