Summary of Risk Management Plan for Adempas

This is a summary of the risk management plan (RMP) for Adempas. The RMP details important risks of Adempas, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) associated with Adempas.

Adempas' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Adempas should be used.

This summary of the RMP for Adempas should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Adempas RMP.

I. The medicine and what it is used for

Adempas is authorised for (see SmPC for the full indication):

- **Chronic thromboembolic pulmonary hypertension (CTEPH)**

  Adempas is indicated for the treatment of adult patients with World Health Organisation (WHO) Functional Class (FC) II-III with

  - inoperable CTEPH,
  - persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.

- **Pulmonary arterial hypertension (PAH) in adults**

  - Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with PAH with WHO FC II to III to improve exercise capacity.
  - Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

- **Pulmonary arterial hypertension (PAH) in children and adolescents**

  - Adempas is indicated for the treatment of PAH in paediatric patients aged <18 years of age and body weight ≥50 kg with WHO Functional Class (FC) II to III in combination with endothelin receptor antagonists.

Adempas contains riociguat as the active substance and it is given by oral administration.

Further information about the evaluation of Adempas' benefits can be found in the Adempas' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/adempas#assessment-history-section

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Adempas, together with measures to minimise such risks and the proposed studies for learning more about Adempas' risks, are outlined below.

Routine risk minimization measures for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the medicinal product. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI-1: Important identified risks, important potential risks, and important missing information associated with Adempas

Important identified risks	None
Important potential risks	Bone safety in patients <18 years old
Missing information	None

II.B Summary of important risks

Table Part VI-2 : Important potential risk: Bone safety in patients <18 years old

Evidence for linking the risk to the medicine	The inclusion of bone safety in patients <18 years old as an important potential risk was based on pre-clinical data. The available clinical evidence

	was considered too limited to conclude on this potential safety concern. The long-term extension phase of the clinical study is still ongoing.
Risk factors and risk groups	None
Risk minimisation measures	Routine risk minimisation measures
Additional pharmacovigilance activities	PATENT CHILD Long Term Extension study

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Adempas.

II.C.2 Other studies in post-authorisation development plan

PATENT CHILD Phase III Study – Long term Extension (SN 15681)

Purpose of the study:

PATENT-CHILD was a 24-participant trial designed to evaluate PK, safety, and tolerability with exploratory efficacy endpoints over a time period of 24 weeks (main phase). The LTE phase is ongoing. The primary safety outcome of this study was incidence of TEAEs and TESAEs as well as discontinuations from the study. Also, part of the primary safety outcome was the analysis of the change of bone age from baseline to the Week 24 compared to chronological age, and bone morphology. This was done by means of X-ray of the left hand and wrist.

PATENT CHILD LTE:

Bone age and bone morphology assessment is continued during the LTE at 12 months intervals until growth velocity has plateaued and growth plates are closed. In addition, any bone changes as assessed by the investigator are to be reported as Adverse Events of Special Interest (AESI).