LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pahrilan,
(riociguat)

SE/H/2695/001-005/DC

This module reflects the scientific discussion for the approval of Pahrilan. The procedure was finalised at 2026-04-29. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Ridecia, Riociguat ELPEN, Riociguat Win Medica, Pahrilan, 0,5 mg, 1 mg, 1,5 mg, 2 mg, 2,5 mg, Film-coated tablet.

The active substance is riociguat. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pahrilan belongs to the pharmacotherapeutic group “Antihypertensives (antihypertensives for pulmonary arterial hypertension)”; ATC code: C02KX05

The active substance is riociguat, which 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.

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.

II.2 General comments on the submitted dossier

The applications for Pahrilan, 0,5 mg, 1 mg, 1,5 mg, 2 mg, 2,5 mg, film-coated tablet, are Generic Art. 10(1) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with concerned member states (CMS) as follows:

SE/H/2695/001-005/DC: AT, DE, IT, NL

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Adempas, 0,5 mg, film-coated tablet authorised in the Union since 2014, with Bayer AG as marketing authorisation holder.

The reference product used in the bioequivalence studies is Adempas 1 mg and 2,5 mg, film-coated tablet from Germany with Bayer AG as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Pahrilan are considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Trepulmix and Winrevair.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Trepulmix and Winrevair in the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, does not prevent the granting of the marketing authorisation of Ridecia and others. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. The clinical and the bioanalytical facilities were inspected by the Spanish authority (AEMPS) in 2023. There were critical findings, but these are not considered to affect the reliability of the current studies. No issues regarding GCP have been identified during the assessment of the submitted bioequivalence studies. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of riociguat are well known. As riociguat is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The Applicant has identified a previously regulatory approved ERA (for Adempas) and concludes that the environmental risk conclusions of that reference ERA are also applicable for the proposed product. The conclusions of the Applicant are supported.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Pahrilan (riociguat) with the reference product Adempas.

Pharmacokinetic properties of the active substance
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%.

Linearity: Riociguat pharmacokinetics are linear from 0.5 to 2.5 mg.

Elimination: Elimination half-life is about 7 hours in healthy subjects and about 12 hours in patients.

Study C1B04055 (1 mg)
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Riociguat, 1 mg, film-coated tablet with Adempas, 1 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of riociguat were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 22 May 2024 and 01 June 2024.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for riociguat, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**630.776 ± 206.561**	**46.037 ± 11.544**	**1.625 (0.500-5.000)**
Reference	**620.411 ± 195.495**	**49.781 ± 9.653**	**1.000 (0.500-3.500)**
***Ratio (90% CI)**	**101.07 (96.49-105.88)**	**91.24 (85.69-97.14)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study C1B02639 (2.5 mg)

Methods

This was a single-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Riociguat, 2.5 mg, film-coated tablet with Adempas, 2.5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of riociguat were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 20 May 2024 and 30 May 2024.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for riociguat, n=44.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1187.893 ± 480.965**	**105.615 ± 26.869**	**1.500 (0.500-4.000)**
Reference	**1145.383 ± 397.046**	**110.072 ± 23.783**	**1.250 (0.500-3.500)**
***Ratio (90% CI)**	**101.01 (94.92-107.48)**	**95.26 (90.02-100.81)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 0.5 mg, 1.5 mg and 2 mg.

Discussion and overall conclusion

The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence

(CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence studies, Ridecia is considered bioequivalent with Adempas.

Absence of studies with the additional strengths of 0.5 mg, 1.5 mg and 2 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of riociguat is linear between 0.5 mg and 2.5 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
G.L. Pharma GmbH
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted an updated risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pahrilan.
The RMP has been amended in accordance with the current version RMP of the originator product Adempas (V9.3, DLP 19-Sep-2024, date of final sign off 04-Mar-2025, Summary last updated on the EMA website on 05-Aug-2025).

Part II Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Bone safety in patients <18 years old
Missing information	• None

The proposed summary of safety concerns is aligned with that of the reference product Adempas, which is endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.
However, in line with the RMP of the originator product, a specific follow-up questionnaire is proposed to obtain structured information on the following safety concern:
- Bone safety in patients <18 years old

The specific follow-up form is provided in Annex 4 of the RMP.

NB: There is an additional pharmacovigilance activity ongoing for the reference product, ie. the PATENT CHILD phase III Study – Long term Extension (SN 15681). However, for generic application products, such as Pahrilan, no such study is requested.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
SE/H/2695/001-005/DC (Pahrilan):
The submitted Risk Management Plan, version 0.2 signed 16/09/2025, is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Pahrilan, is found adequate. There are no objections to approval of Pahrilan, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 **Assessment of User Testing**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
In conclusion, the user test is considered acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-