LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rivaroxaban ALIUD
(rivaroxaban)

SE/H/2175/01-03/DC

This module reflects the scientific discussion for the approval of Rivaroxaban ALIUD. The procedure was finalised on 2022-11-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Rivaroxaban ALIUD, 15 mg, 20 mg, 15 mg + 20 mg, capsule, hard.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Rivaroxaban ALIUD, 15 mg, 20 mg, 15 mg + 20 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, STADA Arzneimittel AG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS):
SE/H/2173/01-03/DC: AT, BE, DE, DK, EE, ES, FI, FR, IE, IS, LT, LU, LV, NL, NO, PT, RO
SE/H/2174/01-03/DC: DE, IT
SE/H/2175/01-03/DC: CZ, EL, HR, HU, PL, SK

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xarelto, 10 mg, film-coated tablet authorised in the EU since 2008, with Bayer AG as marketing authorisation holder.

The reference product used in the bioequivalence study is Xarelto, 20 mg, film-coated tablet from Germany with Bayer AG as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Rivaroxaban ALIUD is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Rivaroxaban ALIUD from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Rivaroxaban ALIUD with the reference product Xarelto.

Pharmacokinetic properties of the active substance
Absorption: Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake. Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food.

Linearity: Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Elimination: Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Study 0922-18
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (33 completed), comparing Rivaroxaban, 20 mg, capsule with Xarelto, 20 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of rivaroxaban were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 13 May 2019 and 22 May 2019.

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 rivaroxaban, n=33.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3442.830 ± 816.1108**	**489.906 ± 119.6342**	**5.500 (3.000 - 6.017)**
Reference	**3491.568 ± 912.4124**	**489.015 ± 106.0093**	**4.333 (1.000 - 5.500)**
***Ratio (90% CI)**	**100.4 (95.77 - 105.22)**	**100.0 (94.61 - 105.78)**	**-**
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 strength of 15 mg.

Discussion and overall conclusion

The bioequivalence study and its 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**). The study design was also in accordance with the EMA Rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg product-specific bioequivalence guidance (EMA/CHMP/160650/2016). The bioanalytical method was adequately validated.

Absence of studies with the additional strength of 15 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) are fulfilled and since dose-proportionality has been demonstrated for 10 mg, 15 mg and 20 mg tablets under fed conditions.

Based on the submitted bioequivalence study, Rivaroxaban ALIUD is considered bioequivalent with Xarelto.

Pharmacodynamics/Clinical efficacy/Clinical safety

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

Risk Management Plan

The MAH has submitted a 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 Rivaroxaban ALIUD.

Safety specification

The MAH has submitted the version 1.2 signed RMP dated 2022-10-04 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal toxicity
Missing information	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP3A4 or P gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, and Systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) and acute coronary syndrome (ACS) in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, including the specific ADR follow-up questionnaires concerning liver-related adverse events and renal impairment/renal failure.

Risk minimisation measures

Routine RMM is suggested for all except haemorrhage. As an additional risk minimisation measure an educational pack will be provided containing SmPC, Prescriber's Guide and Patient Alert Card to address the safety concern of haemorrhage.

Educational Material
- Summary of Product Characteristics - Prescriber Guide - Patient Alert Card Objectives: These materials should ensure that prescribers are informed and the patients understand and acknowledge the risk of haemorrhage associated with rivaroxaban use. Rationale for the additional risk minimisation activity: The educational material is expected to raise the awareness and to minimize the risk of haemorrhage identified in the frame of the EU Risk Management Plan established for the reference medicinal product.

See also section VI.3 below regarding conditions pursuant to Article 21a of Directive 2001/83/EC.

Summary of the RMP

The submitted Risk Management Plan, version 1.2 signed 2022-10-04 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.

V. USER CONSULTATION

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 package leaflet 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products Rivaroxaban ALIUD is found adequate. There are no objections to approval of Rivaroxaban ALIUD, 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 ratio is considered positive and Rivaroxaban ALIUD, 15 mg, 20 mg, 15 mg + 20 mg, capsule, hard, is recommended for approval.
See below regarding conditions pursuant to Article 21a of Directive 2001/83/EC.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC
Additional risk minimisation measures (including educational material)
The educational material should contain the following key elements:

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of haemorrhage during treatment with Rivaroxaban and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The MAH must agree on the content and format of the Prescriber Guide together with a communication plan, with the national competent authority prior to distribution of the educational pack. The Prescriber Guide should contain the following key safety messages:
- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg capsules with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg capsules with food
  - Necessity to carry the Patient Alert Card with them at all times
  - The need to inform Health Care Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure.

Patient Alert Card is made directly accessible to the patient. The exact form of distribution channel will be discussed with each national competent authority.

VII. APPROVAL

The decentralised procedure for Rivaroxaban ALIUD, 15 mg, 20 mg, 15 mg + 20 mg, capsule, hard was positively finalised on 2022-11-24.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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