LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rivaroxaban Bluefish
(rivaroxaban)

SE/H/2343/01-04/DC

This module reflects the scientific discussion for the approval of Rivaroxaban Bluefish. The procedure was finalised on 2024-01-16. 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 Bluefish, 10 mg, 15 mg, 20 mg, 15 mg + 20 mg, Film-coated tablet.

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 Bluefish, 10 mg, 15 mg, 20 mg, 15 mg + 20 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, DK, ES, FR, IE, IS, NO, PL, PT and UK(NI) as concerned member states (CMS).

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 Union since 2008, with Bayer AG as marketing authorisation holder.

The reference product used in the bioequivalence studies is Xarelto 10 mg film-coated tablet and 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

Pharmacology/Pharmacokinetics/Toxicology
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 Bluefish 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 Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Rivaroxaban film-coated tablets 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.

Oral absorption of rivaroxaban is almost complete and the oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.

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.

As stated in the product-specific bioequivalence guideline for rivaroxaban, the food recommendations are different for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths.

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
The terminal half-life is 5-9 hours in young individuals, and 11-13 hours in the elderly.

Study 015-21 (20 mg, fed state)

Methods
This was an open label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study conducted in 20 healthy volunteers, comparing Rivaroxaban, 20 mg, film-coated tablets with Xarelto, 20 mg, film-coated tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of rivaroxaban were determined with an 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 23-Oct-2021 and 03-Nov-2021.

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=19.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3127.20 ± 580.77**	**387.94 ± 54.41**	**3.67 (1.0 - 10.0)**
Reference	**3216.04 ± 609.86**	**398.02 ± 57.80**	**4.33 (1.0 - 10.0)**
***Ratio (90% CI)**	**97.29 (91.80 - 103.12)**	**97.67 (90.18 - 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%.

Study 052-22 (10 mg, fasting)
Methods
This was an open label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study conducted in 25 healthy volunteers, comparing Rivaroxaban, 10 mg, film-coated tablets with Xarelto, 10 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of rivaroxaban were determined with an 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 18-Aug-2022 and 28-Aug-2022.

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 rivaroxaban, n=25.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1509.15 ± 274.27**	**176.04 ± 40.39**	**2.67 (0.75 - 4.50)**
Reference	**1472.18 ± 331.11**	**171.07 ± 43.66**	**2.00 (0.50 - 4.50)**
***Ratio (90% CI)**	**102.98 (98.76 - 107.38)**	**102.65 (94.15 - 111.91)**	**-**

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 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) and the EMA product-specific bioequivalence guidance for rivaroxaban (EMA/CHMP/160650/2016). The bioanalytical methods were 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 the pharmacokinetics of rivaroxaban is approximately linear up to 15 mg.

Based on the submitted bioequivalence studies, Rivaroxaban Bluefish is considered bioequivalent with Xarelto.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted, which is acceptable.

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 Bluefish.

Part II Safety specification
The safety concerns of Rivaroxaban Bluefish are aligned with those of the reference product (Xarelto - Risk management plan version 13.4 dated 13 June 2022) and are endorsed.

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

Part III Pharmacovigilance Plan
Beyond routine pharmacovigilance activities, the applicant proposes specific adverse reaction follow-up questionnaires for the following AEs:

- Liver-related adverse events
- Renal impairment/renal failure

No additional pharmacovigilance activities are proposed, which is endorsed.

Part V Risk minimisation measures
Beyond routine risk minimisation measures (including safety messages in the SmPC and PL, Limited package supply and Prescription status), the applicant proposes additional risk minimisation measures with respect to the safety concern "Haemorrhage". Educational material for prescribers and Patient alert card for patients are proposed, with the aim to increase awareness among prescribers/patients and reduce the risk of bleeding events.
The proposed pharmacovigilance activities and risk minimisation activities are endorsed.

Part VI Summary of the RMP
The proposed RMP for Rivaroxaban Bluefish is adequately summarised by the applicant.

Conclusions of the RMP assessment
The submitted RMP, version 1.1 dated 2023-06-09, 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

A bridging report, referring to the user tested package leaflets of Xarelto film-coated tablets (content) and Venlafaxine Bluefish prolonged-release capsules (layout), has been provided.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Rivaroxaban Bluefish, is found adequate. There are no objections to approval of Rivaroxaban Bluefish, 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.

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 MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of bleeding 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 the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory.

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 tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and 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 tablets 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.

- The Patient alert card should contain the following key safety messages:
  - Signs or symptoms of bleeding and when to seek attention from a health careprovider.
  - Importance of treatment compliance

- The need for intake of the 15 mg and 20 mg tablets 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.

- **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

VII. APPROVAL

The decentralised procedure for Rivaroxaban Bluefish, 10 mg, 15 mg, 20 mg, 15 mg + 20 mg, Film-coated tablet was positively finalised on 2024-01-16.

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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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