LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rivaroxaban Jubilant
(rivaroxaban)

SE/H/2548/01-04/DC

This module reflects the scientific discussion for the approval of Rivaroxaban Jubilant. The procedure was finalised on 2025-08-19. 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 Jubilant, 2.5 mg, 10 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 Jubilant, 2.5 mg, 10 mg, 15 mg, 20 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE and ES 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, 2.5 mg and 15 mg film-coated tablets from DE and Xarelto, 10 mg and 20 mg, film-coated tablets from NL with Bayer AG as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Rivaroxaban Jubilant 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 Jubilant from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted four bioequivalence studies (2.5 mg fasting, 10 mg fasting, 15 mg fed and 20 mg fed) comparing Rivaroxaban Jubilant with the reference product Xarelto.

Pharmacokinetic properties of the active substance
Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and 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. Rivaroxaban Jubilant 2.5 mg and 10 mg tablets can be taken with or without food.

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 Jubilant 15 mg and 20 mg are to be taken with food.

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. This is more marked in fasting state than in fed state.

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 C1B04967 - 2.5 mg fasting
Methods
This was a single-dose, two-way crossover study conducted in 42 healthy volunteers, comparing Rivaroxaban Jubilant, 2.5 mg, film-coated tablet with Xarelto, 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 rivaroxaban 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 24 December 2024 and 03 February 2025.

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=42.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**380.6 ± 105.9**	**67.1 ± 15.3**	**2.00 (0.67-4.50)**
Reference	**372.5 ± 92.5**	**68.2 ± 17.4**	**2.33 (0.67-4.50)**
***Ratio (90% CI)**	**101.29 (96.53-106.28)**	**98.40 (93.40-103.67)**	**-**

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 C1B03780 - 10 mg fasting
Methods
This was a single-dose, two-way crossover study conducted in 50 healthy volunteers, comparing Rivaroxaban Jubilant, 10 mg, film-coated tablet with Xarelto, 10 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 rivaroxaban 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 28 December 2023 and 14 February 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 rivaroxaban, n=49.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1254.6 ± 277.6**	**167.9 ± 42.3**	**2.00 (0.50-4.50)**
Reference	**1352.9 ± 382.6**	**193.0 ± 60.4**	**2.33 (0.67-6.00)**
***Ratio (90% CI)**	**94.83 (90.69-99.16)**	**88.78 (83.58-94.30)**	**-**

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 C1B04968 - 15 mg fed
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing

Rivaroxaban Jubilant, 15 mg, film-coated tablet with Xarelto, 15 mg, film-coated tablet 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 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 14 January 2025 and 21 January 2025.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for rivaroxaban, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1782.9 ± 392.6**	**290.2 ± 68.4**	**3.67 (1.33-4.50)**
Reference	**1777.0 ± 456.3**	**293.8 ± 62.0**	**3.00 (0.67-4.50)**
***Ratio (90% CI)**	**101.09 (95.79-106.69)**	**98.42 (93.42-103.69)**	**-**

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 C1B03781 - 20 mg fed
Methods
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Rivaroxaban Jubilant, 20 mg, film-coated tablet with Xarelto, 20 mg, film-coated tablet 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 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 26 December 2023 and 13 February 2024.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 4 below.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for rivaroxaban, n=40.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2604.4 ± 553.0**	**370.1 ± 60.9**	**2.83 (0.75-4.50)**
Reference	**2529.9 ± 556.5**	**366.1 ±62.4**	**2.33 (0.75-5.00)**
***Ratio (90% CI)**	**103.16 (99.25-107.23)**	**101.20 (97.77-104.74)**	**-**

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

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%.

Discussion and overall conclusion

For rivaroxaban there is a different food effect for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths resulting in different food recommendations. Therefore, studies with two strengths are required, one fasting study should be conducted for the lower strengths and one fed study for the higher strengths according to the product-specific bioequivalence guidance for rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg (EMA/CHMP/160650/2016).

The initial biowaiver for the 2.5 mg and 15 mg strengths was not sufficiently justified by the provided data. The applicant conducted bioequivalence studies for the remaining two strengths, 2.5 mg and 15 mg during clock-stop.

Bioequivalence studies have been submitted for the 2.5 mg, 10 mg (fasting state), 15 mg and 20 mg (fed state) strengths.

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 in line with the product-specific bioequivalence guidance for rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg (EMA/CHMP/160650/2016). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Rivaroxaban Jubilant 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 Jubilant.

Part II Safety specification

The MAH has submitted the version 3.0 RMP dated 02-June-2025 and proposed the following summary of safety concerns:

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 prosthetic heart valve

Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are in line with the reference product (except for safety concerns regarding granules for oral suspension since that pharmaceutical form is not applied for) and considered appropriate.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning liver-related adverse events and renal impairment/renal failure, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant which is endorsed.

Part V Risk minimisation measures

Routine risk minimisation is suggested and additional risk minimisation activities (i.e. educational material for prescribers in form of a prescriber guide, and patient alert card) are suggested by the applicant for the important identified risk haemorrhage. This is in line with the reference product and is endorsed.
See section VII.3 further down for details regarding the key elements of the educational material.

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

Conclusion RMP assessment
The submitted Risk Management Plan, version 3.0 signed 02-June-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.

V. USER CONSULTATION

The package leaflet for 15 mg and 20 mg 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.

A user consultation with target patient groups on the package information leaflet (PL) for 2.5 mg and 10 mg has been performed on the basis of a bridging report making reference to Rivaroxaban Jubilant 15 mg and 20 mg, for which products are included in this procedure.
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, is found adequate. There are no objections to approval of Rivaroxaban, 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 educational material should contain the following key elements:

  The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Rivaroxaban Jubilant. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Rivaroxaban Jubilant 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 [Text included in Annex III]

  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 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 that is included in each pack, with them at all times
  ➢ The need to inform Health Care Professionals that they are taking Rivaroxaban Jubilant if they need to have any surgery or invasive procedure.

  The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III.

- **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 Jubilant, 2.5 mg, 10 mg, 15 mg, 20 mg, film-coated tablet was positively finalised on 2025-08-19.

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SWEDISH MEDICAL PRODUCTS AGENCY

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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