LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rivaroxaban Orion
(rivaroxaban)

SE/H/2124/01-04/DC

This module reflects the scientific discussion for the approval of Rivaroxaban Orion. The procedure was finalised on 2023-02-23. 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 Orion, 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 Orion, 2,5 mg, 10 mg, 15 mg, 20 mg Film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, NO, FI, PL, CZ, HU, EE, LT and LV as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xarelto, 2,5 mg, 10 mg, 15 mg, 20 mg, Film-coated tablet, authorised in UNION since 2008, with Bayer AG as marketing authorisation holder.

The reference product used in the bioequivalence studies is Xarelto 2.5 mg and 20 mg from Romania and Xarelto 10 mg 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 Orion 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 Orion from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted three bioequivalence studies comparing Rivaroxaban Orion 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 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 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 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. This is more marked in fasting state than in fed state.

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 NCS-644-18-CS – 2.5 MG FASTING
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Rivaroxaban, 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 72 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 10 DEC 19 and 16 JAN 20.

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=44.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**466.255 ± 95.381**	**69.429 ± 14.723**	**2.667 (1.000-4.500)**
Reference	**460.692 ± 89.996**	**69.115 ± 12.168**	**2.667 (0.500-4.500)**
***Ratio (90% CI)**	**100.63 (97.34-104.0)**	**99.61 (94.92-104.54)**	**-**

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 NCS-657-19-CS – 10 MG FASTING
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Rivaroxaban, 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 72 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 29 MAR 19 and 06 MAY 19.

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=43 (Test: C_{max} and AUC_{0-t}; Reference: C_{max}) and n=42 (Reference: AUC_{0-t}).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1748.930 ± 324.139**	**194.961 ± 50.601**	**3.333 (0.500-4.500)**
Reference	**1798.524 ± 352.798**	**199.439 ± 53.507**	**2.333 (1.000-5.000)**
***Ratio (90% CI)**	**97.24 (93.02-101.66)**	**98.87 (89.77-108.91)**	**-**

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%.

Study NCS-604-18-CS – 20 MG FED

Methods

This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Rivaroxaban, 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 72 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 10 JAN 19 and 07 FEB 19.

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=44.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3875.122 ± 854.510**	**427.914 ± 96.555**	**5.500 (1.000-6.000)**
Reference	**3949.673 ± 919.630**	**442.368 ± 86.947**	**5.000 (1.000-6.000)**
***Ratio (90% CI)**	**98.55 (95.59-101.60)**	**96.31 (91.34-101.56)**	**-**

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 rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg product-specific bioequivalence guidance (EMA/CHMP/160650/2016) recommends two single-dose studies, one single-dose study under fasting conditions with the 10 mg strength and one single-dose study under fed conditions with the 20 mg strength.

Since there is a different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths, fasting study should be conducted for the lower strengths, and fed study for the higher strengths. Due to the different food effect at different strengths, studies with two strengths are required.

The number and design of submitted studies are acceptable. The studies with 10 mg and 20 mg strengths are submitted in line with EMA's product-specific guidance for rivaroxaban.

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 **). 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 strengths, as described in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **) are fulfilled and rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality under fed conditions.

Based on the submitted bioequivalence studies, Rivaroxaban Orion 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 Orion.

Safety specification
The applicant has submitted the version 1.2 RMP dated 2023-01-03 and proposed the following safety concerns:

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP 3A4 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, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years

The proposed safety concerns given by the applicant are in accordance with those listed for the reference product Xarelto in the RMP v11.4 dated 01 August 2018 (Bayer AG) published on European public assessment report (EPAR). The proposed safety concerns are acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested by the applicant and with additional specific adverse reaction follow-up queries for liver-related adverse events and renal impairment/failure. This is endorsed.

Risk minimisation measures
The applicant has provided the following information on risk minimisation measures:

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Haemorrhage	Routine risk minimisation measures: Information in SmPC sections 4.3, 4.4 and 4.8, and PL sections 2 and 4. Additional risk minimisation measures: Educational pack	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Important potential risk: Embryo-fetal toxicity	Routine risk minimisation measures: Information in SmPC sections 4.3, 4.6 and 5.3, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Missing information: Patients with severe renal impairment (CrCl < 30 mL/min)	Routine risk minimisation measures: Information in SmPC sections 4.2 and 4.4, and PL sections 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up query form for adverse reactions
Missing information: Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	Routine risk minimisation measures: Information in SmPC sections 4.4 and 4.5, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimisation measures: Information in SmPC sections 4.3 and 4.6, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Pregnant or breast-feeding women	Routine risk minimisation measures: Information in SmPC sections 4.3 and 4.6, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Missing information: Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimisation measures: Information in SmPC section 4.4 and 4.8, and PL sections 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Missing information: Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Missing information: Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine risk minimisation measures: Information in SmPC sections 4.2, 4.3 and 5.2, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up query form for adverse reactions
Missing information: Patients < 18 years	Routine risk minimisation measures: Information in SmPC section 4.2, and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

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. This is in

accordance with condition for the reference product. See also section VI below regarding conditions pursuant to Article 21a of Directive 2001/83/EC.

The applicant has stated that the distribution path will include mailing of the printed material and/or electronic access to the material. It is also mentioned that the patient alert card will be included in the packages of each medicinal product.

Summary of the RMP

The MAH has satisfactorily responded to the question raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 1.2 signed 2023-01-03 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 user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to the centrally authorised medicinal product Xarelto, 2,5 mg, 10 mg, 15 mg, 20 mg, film-coated tablets.

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 Orion, is found adequate. There are no objections to approval of Rivaroxaban Orion, 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. For conditions pursuant to Article 21a of Directive 2001/83/EC, see below.

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 the launch of the product, targeting all physicians who are expected to prescribe/use rivaroxaban. The educational pack is aimed at increasing awareness about the risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk.

The content and format of the educational material, together with a communication plan, should be agreed with the national competent authority prior to distribution of the educational pack.

- The physician educational pack should contain:
    - The Summary of Product Characteristics
    - Prescriber Guide
    - Patient Alert Cards
- 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 be counselled about:
        - 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.
- 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.

VII. APPROVAL

The decentralised procedure for Rivaroxaban Orion, 2,5 mg, 10 mg, 15 mg, 20 mg, Film-coated tablet was positively finalised on 2023-02-23.

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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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