COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rivaroxaban Amarox 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets (rivaroxaban)

NL/H/5283/001-004/DC

Date: 20 October 2022

This module reflects the scientific discussion for the approval of Rivaroxaban Amarox 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. The procedure was finalised at 3 August 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban Amarox 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets, from Amarox Pharma B.V.

The product is indicated for:

2.5 mg
Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

10 mg
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

15 mg
Adults
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

20 mg
Adults
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets, which have been registered in the EEA by Bayer AG since 30 September 2008 via a centralised procedure (EMEA/H/C/000944).

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

All four strengths of Rivaroxaban Amarox are round shaped, biconvex, film-coated tablets.

- The 2.5 mg tablets contain 2.5 mg of rivaroxaban, are white to off-white and have “R20” debossed on one side and “H” on the other side.
- The 10 mg tablets contain 10 mg of rivaroxaban, are orange and have “R21” debossed on one side and “H” on the other side.
- The 15 mg tablets contain 15 mg of rivaroxaban, are grey and have “R22” debossed on one side and “H” on the other side.
- The 20 mg tablets contain 20 mg of rivaroxaban, are light grey and have “R23” debossed on one side and “H” on the other side.

The tablets are packed in clear PVC/PVDC-Aluminium foil blisters or HDPE bottles with child resistant plastic caps.

The excipients for the 2.5 mg tablets are:

- *Tablet core* - cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose (2910), sodiumlauril sulfate and magnesium stearate.
- *Film-coating* - hypromellose (2910), titaniumdioxide (E171), macrogol (E1521).

The excipients for the 10 mg tablets are:

- *Tablet core* - cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose (2910), sodiumlauril sulfate and magnesium stearate.
- *Film-coating* - hypromellose (2910), titanium dioxide (E171), macrogol (E1521), yellow iron oxide (E172), red iron oxide (E172).

The excipients for the 15 mg and 20 mg tablets are:

- *Tablet core* - cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose (2910), sodiumlauril sulfate and magnesium stearate.
- *Film-coating* - hypromellose (2910), macrogol (E1521), titanium dioxide (E171), black iron oxide (E172) and yellow iron oxide (E172).

The 2.5 mg and 10 mg tablet cores and the 15 mg and 20 mg tablet cores are quantitatively proportional.

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white powder that is practically insoluble in water. Rivaroxaban incorporates one stereogenic centre in its structure and is a pure enantiomer. Different polymorphic forms of rivaroxaban are known, the polymorphic form used is referred to as polymorphic form-I.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of five chemical transformation steps with four isolated intermediates and a final purification step. No class 1 solvents or heavy metal catalysts are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur with additional requirements for particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) which is in accordance with applicable European guidelines. No clear trends or changes were seen in any of the tested parameters at both storage conditions. Based on the data submitted, a retest period could be granted of 5 years when stored at 25°C and in light-resistant containers.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference products, optimization of the formulation and dissolution method development. The choice of the dissolution method is justified, and the discriminatory power of the method was demonstrated. Two bioequivalence studies were performed, one study with the 10 mg tablets and one with the 20 mg tablets. For the 2.5 mg and 15 mg strengths a biowaiver was requested and granted. It has been sufficiently demonstrated that all four strengths of tablets can be adequately administered per gastric tube.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is a standard process consisting of blending of ingredients, wet granulation, compression, coating and packaging. Process validation data on the product have been presented for three production scaled batches per strength.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for the iron oxides which comply with EU Regulation 231/2012. Functionality-related characteristics are controlled for several of the tablet core excipients. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average mass, water content, dissolution, uniformity of dosage units, assay, related substances, dissolution, microbiological quality and identification of colorants. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Based on the provided data on impurities in the active substance and the provided nitrosamine risk evaluation it is concluded that there is currently no risk for nitrosamine impurities in the drug product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three product scales batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for 3 production scaled batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in line with the ICH stability guideline. The batches were tested for description, water content, assay, dissolution, related compounds and microbiological examination. A slight increase in water content is observed. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The proposed shelf-life of 36 months without any special storage conditions is acceptable.

In use stability of 90 days after first opening of the HDPE container has been adequately demonstrated.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSE/BSE free certificates of sodium laurel sulfate have been provided. The milk used to produce lactose monohydrate is derived under the same conditions as milk collected for human consumption and the calf rennet is produced in accordance with the applicable guidelines. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rivaroxaban Amarox has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban Amarox is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xarelto which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical

overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rivaroxaban is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban Amarox 10 mg and 20 mg, film-coated tablets (Amarox Pharma B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference products Xarelto 10 mg and 20 mg film-coated tablets (Bayer AG, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver of strength was requested for the 2.5 mg strength and for the 15 mg strength. The following conditions are fulfilled:

- The products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- Appropriate *in vitro* dissolution data are available for all strengths at three pH values.
- The strengths are dose proportional.

This is in line with the requirements of the EMA Guideline on Bioequivalence.

Bioequivalence studies

To support the application the applicant has submitted two bioequivalence studies. One single-dose bioequivalence study under fasted conditions of rivaroxaban 10 mg and one single-dose bioequivalence study under fed conditions of rivaroxaban 20 mg. This is in

accordance with the "Rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg product-specific bioequivalence guidance" (EMA/CHMP/160650/2016). The design of the studies is acceptable.

Analytical/statistical methods
The analytical method of both studies has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study 1 (single-dose, fasting, 10 mg tablet)
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 52 healthy male subjects, aged 18-45 years. Each subject received a single dose (10 mg) of one of the 2 rivaroxaban formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected at pre-dose (0.00) and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

Results
All 52 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban 10 mg under fasted conditions.

Treatment N=52	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1085.5 ± 281.0	1116.4 ± 277.1	166.6 ± 40.6	2.00 (0.50 – 4.33)
Reference	1093.9 ± 304.7	1133.7 ± 298.3	170.7 ± 55.5	1.75 (0.75 – 4.33)
***Ratio (90% CI)**	1.00 (0.94– 1.06)	-	0.99 (0.93– 1.05)	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration

**ln-transformed values*

Study 2 (single-dose, fed, 20 mg tablet)
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 34 healthy male subjects, aged

18-45 years. Each subject received a single dose (20 mg) of one of the 2 rivaroxaban formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected at pre-dose (0.00) and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

Results
Ten subjects dropped-out or were withdrawn from the study. Eight subjects experienced mild to moderate adverse events, one subject withdrew due to personal circumstances and one subject did not report to the facility for period two. In total 24 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban 20 mg under fed conditions.

Treatment N=24	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	2691.1± 704.9	2718.0 ± 708.6	372.7 ± 72.9	4.04 (1.25 – 8.03)
Reference	2421.5± 515.3	2457.3 ± 529.2	330.4 ± 68.8	4.04 (0.75 – 10.00)
***Ratio (90% CI)**	1.09 (1.02– 1.18)	-	1.13 (1.04– 1.22)	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rivaroxaban Amarox 10 mg and 20 mg, film-coated tablets are considered bioequivalent with Xarelto 10 mg and 20 mg film-coated tablets

The results of the bioequivalence studies can be extrapolated to the 2.5 mg and 15 mg tablets. All criteria are met to grant a biowaiver for the 2.5 mg and 15 mg strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Amarox.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Patients with severe renal impairment (creatinine clearance [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)

Additional risk minimisation measures

It is considered that additional risk minimisation measures are necessary for the safe and effective use of the product.

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 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 always
    - The need to inform healthcare professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure.

The MAH shall also provide a patient alert card in each medicine pack.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xarelto no new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets (EMEA/H/C/000944) for content and Levetiracetam Hetero 750mg film-coated tablets (PT/H/515/01-04/DC) for the layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rivaroxaban Amarox 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. Xarelto is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting of 28 July 2022, the following was discussed:

- Dissolution data of three stability batches obtained after 38 months storage at long term conditions were submitted. All batches complied with the tightened acceptance criterion of NLT 80%. The updated stability data support the claimed shelf life of 36 months.
- The gastric tube study was repeated with the 2.5 mg and 10 mg strengths of the test and reference product. The provided data support the instructions regarding crushing of tablets in the SmPC.
- The risk for presence of nitrosamine impurities has not been excluded nor mitigated. At the time of the board meeting the benefit/risk balance of Rivaroxaban Amarox was therefore considered negative. After the board meeting additional data were provided and it was concluded that there is currently no risk for nitrosamine impurities in the drug product.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivaroxaban Amarox 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 3 August 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse