COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tenarox 10 mg, 15 mg and 20 mg film-coated tablets (rivaroxaban)

NL License RVG: 128109, 128111 & 128112

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This module reflects the scientific discussion for the approval of Tenarox 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised on 26 July 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Tenarox 10 mg, 15 mg and 20 mg film-coated tablets, from Maddox Pharma Swiss B.V.

The product is an anticoagulant medicine (a medicine that prevents blood clotting) indicated:

- to treat deep vein thrombosis (DVT, a blood clot in a deep vein, usually in the leg) and pulmonary embolism (a clot in a blood vessel supplying the lungs), and to prevent DVT and pulmonary embolism from recurring in adults;
- to prevent venous thromboembolism (VTE, the formation of blood clots in the veins) in adults who are undergoing surgery to replace a hip or knee;
- to treat VTE and prevent VTE from recurring in children and adolescents aged less than 18 years;
- to prevent stroke (caused by a blood clot in the brain) and systemic embolism (a blood clot in another organ) in adults with non-valvular atrial fibrillation (irregular rapid contractions of the upper chambers of the heart);
- to prevent atherothrombotic events (such as heart attack, stroke or death from heart disease) in adults:
    - after an acute coronary syndrome, when it is used with an antiplatelet medicine (which prevents the formation of blood clots). Acute coronary syndrome consists of conditions such as unstable angina (a severe type of chest pain) and heart attack;
    - at high risk of ischaemic events (problems caused by restricted blood supply) who have coronary artery disease (disease caused by obstructed blood supply to the heart muscle) or peripheral artery disease (disease caused by defective blood flow in the arteries). It is used with aspirin.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Xarelto 10, 15 and 20 mg film-coated tablets, which has been registered in the EU via a centralised procedure (EU/1/08/472).

II. QUALITY ASPECTS

II.1 Introduction

Tenarox are film-coated tablets containing as active substance 10 mg, 15 mg or 20 mg rivaroxaban. The tablets are round biconvex, with a diameter of 7 mm or 8 mm, with a pink, red or dark red colour and marked with 'C02', 'C03' or 'C04' on one side respectively.

The excipients are:
Tablet core - powdered cellulose, lactose monohydrate, crospovidone, copovidone, sodium laurilsulfate, anhydrous colloidal silica and magnesium stearate.

Film-coating – (partly hydrolysed) polyvinyl alcohol, titanium dioxide (E171), macrogol, talc and red iron oxide (E172).

The 15 mg and 20 mg tablet strengths are dose proportional.

The tablets are packed in polyvinylidene chloride/polyvinyl chloride/aluminium (PVdC/PVC/Al) blisters, high-density polyethylene (HDPE) bottles with a sealed low-density polyethylene (LDPE) cap (Duma Special) or HDPE bottles with a sealed polypropylene (PP) cap (Duma Twist Off) with desiccant.

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, practically insoluble in water. The active substance 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. Rivaroxaban is supplied by two different suppliers. For both suppliers the ASMF procedure is used.

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.

<u>Manufacturing process</u>
Site I
The manufacturing process consists of five chemical transformation steps with four isolated intermediates and a final purification step. The process starts with two starting materials. The third starting material is introduced in the last step prior to the purification step. No class 1 solvents or heavy metal catalysts are used. In the last purification step an organic

solvent is used. The final drug substance is micronised. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Site II
The manufacturing process consists of four chemical transformation steps with three isolated intermediates, followed by a purification step. The process starts with two starting materials. The third starting material is introduced in the third step of the process. No class 1 solvents or heavy metal catalysts are used. In the last purification step an organic solvent is used. Milling or micronisation is performed as per customer requirement. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is in line with the Ph.Eur., with additional requirements for residual solvents, impurities and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for four batches from site I and for and three batches from site II.

Stability of drug substance
Site I
Stability data on the active substance have been provided for at least six production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

Site II
Stability data on the active substance have been provided for four production scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 4 years when stored under the stated conditions.

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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference products, defining of a quality target product profile (QTPP), optimisation of the formulation and dissolution method development. The choice of the dissolution method is justified and its discriminatory power was demonstrated. Bioequivalence (BE) studies have been performed with the 10 mg and 20 mg product versus their respective reference product strengths. The test batches used in the BE study were manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative

dissolution testing at three pH's has been successfully studies in support of the biowaiver for the 15 mg product strength. The pharmaceutical development of the product been adequately performed.

Manufacturing process

The manufacturing process is a standard process consisting of blending of ingredients, dry granulation, compression, coating and packaging. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches per strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements, except for cellactose 80 (lactose monohydrate and powdered cellulose) that complies with in-house requirements and iron oxide that complies 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, uniformity of dosage units, average tablet mass, assay, related substances, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 4-5 pilot scale 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 at least three production scaled batches per strength stored at 25°C/ 60% RH (18-24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The proposed shelf-life of 24 months without any special storage conditions is justified and with a temperature storage restriction 'Store below 30°C' for the 15 mg tablets packed in blisters is justified.

The product was shown to be very stable in an open container stability study and no in-use shelf-life is needed.

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

The only excipient of animal origin is lactose monohydrate (part of cellactose 80). Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and 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 MEB considers that Tenarox 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 Tenarox 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 MEB 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 MEB agreed that no further clinical studies are required, besides the 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 Tenarox 10 mg and 20 mg film-coated tablets (Maddox Pharma Swiss B.V., Netherlands) was compared with the pharmacokinetic profile of the reference product Xarelto 10 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 study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The MAH was granted a biowaiver for *in vitro* bioequivalence studies for the 15 mg strength, based on these criteria:

a) the 15 mg and 20 mg strength are manufactured by the same manufacturing process,
b) the qualitative composition of the two strengths is the same,
c) the composition of the strengths are quantitatively proportional,
d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution of the 15 and 20 mg test product was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Study 1 – single dose, 10 mg, under fasted conditions

Design

An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 22-43 years. Each subject received a single dose (10 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water after an overnight fast for 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Rivaroxaban 10 mg may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of rivaroxaban at the 10 mg dose. Therefore, a food interaction study is not deemed necessary for this strength. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Results
Thirty subjects were enrolled and randomised whereof 29 subjects completed the two periods of the study and were eligible for the pharmacokinetic and statistical analysis. One subject was found positive in alcohol breath test during period two admission hence withdrawn from the study.

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

Treatment N=29	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1781 ± 338	1789 ± 337	223 ± 50	2 (0.75 - 4.50)
Reference	1753 ± 365	1764 ± 365	214 ± 59	2 (0.75 - 4.50)
***Ratio (90% CI)**	1.0 (0.97 - 1.1)	-	1.0 (0.97 - 1.1)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – single dose, 20 mg, under fed conditions
Design
An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-43 years. Each subject received a single dose (20 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water after an overnight fast for 10 hours, followed by a high-calorie, high-fat breakfast consumed within the 30 minutes before dosing. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

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. Therefore, according to the SmPC, rivaroxaban 20 mg is to be taken with food.

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

Results
All 28 subjects 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=28	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3229 ± 726	3246 ± 720	433 ± 101	4.5 (1.5 - 12)
Reference	2957 ± 622	2971 ± 620	404 ± 73	3 (1.5 - 5)
***Ratio (90% CI)**	1.0 (1.0 - 1.1)	-	1.0 (0.99 - 1.1)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

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

The results of the study with the 20 mg formulation can be extrapolated to the lower strength of 15 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Tenarox.

Table 3. 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 cytochrome P450 (CYP) 3A4 or p-glycoprotein (P-gp) other than azole antimycotics (e.g. ketoconazole) and human immunodeficiency virus (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 deep vein thrombosis (DVT), Pulmonary embolism (PE), stroke prevention in AF (SPAF) and acute coronary syndrome (ACS) in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

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 two bioequivalence studies 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 on the basis of a bridging report making reference to Xarelto (EU/1/08/472). 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

Tenarox 10 mg, 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xarelto 10, 15 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.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tenarox with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 26 July 2023.

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
Type IA(IN): B.II.b.2.c.1	Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for importation and/or batch release. Not including batch control/testing.	Yes	31-08-2023	Approved	
Art.61(3)	Add English translations of the PIL and labelling to the product information of the above products in order to have bilingual packaging texts.	Yes	02-10-2023	Approved	
Type IB: C.I.2.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product. Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	16-11-2023	Approved	