COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5515/001-005/DC

Date: 13 May 2025

This module reflects the scientific discussion for the approval of Rivaroxaban Macleods 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets. The procedure was finalised on17 January 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

Listofabbreviations

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
DVT	Deep Vein Thrombosis
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
PE	Pulmonary Embolism
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
VTE	Venous Thromboembolism

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for of Rivaroxaban Macleods 2.5 mg, 10 mg, 15 mg, 20 mg and 15mg + 20 mg film-coated tablets, from Macleods Pharma España S.L.U.

The product is indicated for:
2.5 mg
The product, 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.

The product, 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.

15 mg + 20 mg
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

A comprehensive description of the up-to-date 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 decentralised procedure, essential similarity is proven between the new product and the innovator product Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg, which has been registered in the EEA via a centralised procedure (EU/1/08/472) since 30 September 2008.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

II. QUALITY ASPECTS

II.1 Introduction

The three strengths, can be distinguished by the different size, shape, colour and debossing of the tablets

Rivaroxaban Macleods 2.5 mg is a light yellow colour, circular, biconvex, film coated tablet debossed with "J 7" on one side and plain on the other side. The tablet size is approximately 6.1 mm ± 0.2 mm and contains as active substance 2.5 mg of rivaroxaban.

Rivaroxaban Macleods 10 mg is a pink colour, circular, biconvex, film coated tablet debossed with "J 8" on one side and plain on the other side. The tablet size is approximately 6.1 mm ± 0.2 mm and contains as active substance 10 mg of rivaroxaban.

Rivaroxaban Macleods 15 mg is a light red colour, circular, biconvex, film coated tabletsdebossed with "J 9" on one side and plain on the other side. The tablet size is approximately 6.6 mm ± 0.2 mm and contains as active substance 15 mg of rivaroxaban.

Rivaroxaban Macleods 20 mg is a red colour, triangular shape, film coated tablets debossed with "J 10" on one side and plain on the other side. The tablet size is approximately 7.35 X 7.35 X 7.35 mm ± 0.2 mm and contains as active substance 20 mg of rivaroxaban.

The excipients are:
Tablet core

Cellulose, microcrystalline (E 460); lactose monohydrate 200 M; croscarmellose sodium (E 468); silicon, colloidal anhydrous (E 551); hypromellose 5 mPa.s (2910) (E 464); sodium laurilsulphate (E 487); magnesium stearate (E 470b); methylene chloride and isopropyl alcohol.

Film-coat
Hypromellose 6 mPa.s (2910); macrogol 6000 (2.5 mg, 10 mg and 15 mg only); macrogol 400 (2.5 mg, 10 mgand 20 mg only); titanium dioxide (E 171); yellow iron oxide (E 172) (2.5 mg only); red iron oxide (E 172) (10 mg,15 mg and 20 mg only) and purified water.

The 10 mg, 15 mg and 20 mg tablet strengths are dose proportional.

The film-coated tabletsarepacked in aluminium-polyvinyl chloride/polyethylene/polyvinylidene chloride (Alu-PVC/PE/PVdC) blisters. The blisters are packed in cartons.

II.2 DrugSubstance

The active substance is rivaroxaban, an established active substance described in the European Pharmacopoeia (Ph.Eur.).The active substance is a white to yellowish powder, practically insoluble in acetone and water and is non-hygroscopic. Rivaroxaban has one stereogenic centre and is manufactured as the R and S-enantiomer. The active substance shows polymorphism and is manufactured as a stable polymorphic form.

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 in four steps: 3 synthetic steps, one protecting group removal step and one purification step. The synthesis starts from two starting materials. The third starting material is introduced later in the synthesis. The introduction of this third starting materials is followed by two chemical transformation steps. Two reagents are used in the last purification step. No class 1 organic solvents or heavy metal catalysts are used in the process. 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 not completely in line with the Ph.Eur., with additional requirements for related substances, residual solvents, polymorphic identity, particle size and bulk density. 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 three batches.

Stability of drug substance
Stability data on the active substance has been provided for three production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 24 months 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 were the characterisation of the reference product, evaluation of the critical attributes of the drug substance and excipients, formulation and manufacturing optimization studies. The choices of the packaging and manufacturing process are justified. Bioequivalence (BE) studies have been performed with the 2.5 mg, 10 mg and 20 mg strengths versus their respective reference product strengths. The batches used in the BE studies were manufactured according to the finalised composition and manufacturing process at a representative scale. The QC dissolution method has been adequately established for the different strengths in line with the Ph.Eur. rivaroxaban tablets monograph and the discriminatory behaviour has been demonstrated. Comparative dissolution testing at three pH's has been successfully studied in support of the bioequivalence study and the biowaiver for the 15 mg strength. Study data on the physicochemical compatibility of crushed tablets with (naso)gastric tubes, water and apple puree and dose recovery and flush volume for the (naso)gastric tube have been provided.

Manufacturing process
The main steps of the manufacturing process are sifting, dry mixing, binder preparation, granulation (wet mixing), wet milling, drying, sifting and milling, pre-lubrication, lubrication, compression, coating and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches of the minimum batch size of each strength. 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. with several additional requirements for functionality related characteristics. 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 appearance, identification for rivaroxaban and the colourants, loss on drying, dissolution, uniformity of dosage units, related substances, assay, residual solvents and microbiological quality. Except for loss on drying the release and

shelf life limits are identical. Remaining limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three full scaled batches of each 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 three production scaled batches per strength stored at 25°C/ 60% RH (24 - 48 months) and 40°C/75% RH (6 months).The stability was tested in accordance with applicable ICH guidelines. 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 for the 2.5 mg strength and 36 months for the 10 mg, 15 mg and 20 mg strengths. The labelled storage condition is “do not store above 30°C”.

In-use stability data has been provided for the crushed tablets in water and apple puree demonstrating stability for the claimed 4 hours storage period.

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

Scientific data and/or certificates of suitability issued by the EDQM for all excipients 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.

Magnesium stearate is of vegetable origin. Lactose monohydrate is produced from milk of healthy cows, in the same conditions as milk collected for human consumption under regulation 853/2004. The BSE risk in pharmaceutical grade lactose is considered negligible based on EMEA/CPMP /BWP/337 /O2.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rivaroxaban Macleods 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 Macleods is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban film-coated tablets 2.5, 10 mg and 20 mg (Macleods Pharmaceuticals Limited, India) was compared with the pharmacokinetic profile of the reference product Xarelto tablets 2.5 mg, 10 mg and 20 mg (Bayer AG, Deutschland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition (pH 1.0-1.2, 4.5 and 6.8). The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the 15 mg strength was required. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution 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: 2.5 mg Rivaroxaban film-coated tablets under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label, balanced, analyst blind bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 20-42 years. Each subject received a single dose (2.5 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 8days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 14, 18, 24, 30, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

2.5 mg rivaroxaban may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of rivaroxaban. Therefore, a food interaction study is not deemed necessary. 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

24 subjects enrolled in the study. One subject withdrew from the study in period 1 due to adverse event (vomiting and generalised weakness) on advice of the principle investigator. 23 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 2.5 mg under fasted conditions.

Treatment N=23	**AUC_{0-t} (pg.h/mL)**	**$AUC_{0-\infty}$ (pg.h/mL)**	**C_{max} (pg/mL)**	**t_{max} (h)**
Test	518488 ± 163148	524381 ± 163618	64647 ± 18362	2.00 (1.00 - 4.50)
Reference	533190 ± 133515	539073 ± 134193	72204 ± 15889	2.00 (0.50 - 4.50)
***Ratio (90% CI)**	0.97 (0.94 – 1.00)	-	0.89 (0.83 – 0.96)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: 10 mg Rivaroxaban film-coated tablets under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover , open label, balanced, blind, analyst blind bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 21 - 40 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 of at least 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, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 14, 18, 24, 30, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Rivaroxaban may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of rivaroxaban. Therefore, a food interaction study is not deemed necessary. 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
30 subjects enrolled in the study. 30 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 10 mg under fasted conditions.

Treatment N= 30	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1585 ± 301	1617 ± 302	164 ± 38	2.33 (1.00 - 4.50)
Reference	1642 ± 332	1669 ± 341	181± 42	1.84 (0.50 - 4.50)
***Ratio (90% CI)**	0.97 (0.93 – 1.01)	-	0.91 (0.83-0.99)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3: 20 mg Rivaroxaban film-coated tablets under fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover , open label, balanced, analyst blind bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 20-44 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, 30 minutes after a high fat, high calorie breakfast (258.14 kcal carbohydrates, 173.9 kcal protein, 560.88 kcal fat) after an overnight fast of at least 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, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 14, 18, 24, 30 and 36 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.

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
24 subjects enrolled in the study. One subject failed to report for period II due to personal reasons and dropped out. 23 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 20 mg under fed conditions.

Treatment N=23	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	3791± 577	3864 ± 578	454 ± 80	5.5 (1.5 –6.0)
Reference	3744± 531	3818± 541	440± 65	5.0 (1.0–7.0)
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	-	1.03 (0.98 – 1.08)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
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 1-3:
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 Rivaroxaban Macleods 2.5 mg, 10 mg and 20 mg is considered bioequivalent with Xarelto 2.5 mg, 10 mg and 20 mg.

The results of study 3 with 20 mg formulation can be extrapolated to the 15 mg strength, 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 Rivaroxaban Macleods.

Table 4. 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 (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)

The member states 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. The MAH demonstrated through three bioequivalence studies that the pharmacokinetic profile of the product are 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

The package leaflet (PL) of Rivaroxaban Macleods 20 mg film-coated tablets 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 test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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 leaflet (PL) of Rivaroxaban Macleods 2.5 mg, 10 mg and 15 mg film-coated has been performed on the basis of a bridging report making reference to Rivaroxaban Macleods 20 mg film-coated tablets, NL/H/5515/005/DC. 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 Macleods 2.5 mg, 10 mg, 15 mg, 20 mg and 15 mg + 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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.

The Board followed the advice of the assessors.

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 Macleods with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 January 2024.

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
NL/H/5515/001-5/IA/001	Change in the name and/or address of the marketing authorisation holder	Yes	9-01-2025	Approved	N/A