COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Xiltess 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets

(rivaroxaban)

NL/H/5431/001-004/DC

Date: 5 July 2024

This module reflects the scientific discussion for the approval of Xiltess 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised at 21 November 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 Xiltess 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets, from Egis Pharmaceuticals Plc.

The 2.5 mg strength is indicated for:

- co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see SmPC sections 4.3, 4.4 and 5.1).
- co-administered with ASA, 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.

The 10 mg strength is indicated for:

- the 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 (see SmPC section 4.4 for haemodynamically unstable PE patients).

The 15 mg strength is indicated for:

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 (see SmPC section 4.4 for haemodynamically unstable PE patients.)

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.

The 20 mg strength is indicated for:

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 (see SmPC section 4.4 for haemodynamically unstable PE patients.)

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 product Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets which have been registered in the EEA by Bayer Pharma AG through centralised procedure EU/1/08/472/001-021, 023-038 since 30 September 2008.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania and the Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Rivaroxaban Denk is a round biconvex film-coated tablet:

- The 2.5 mg strength is a light pink coloured film-coated tablet engraved with a ‘E841’ sign on one side. Each tablet contains 2.5 mg rivaroxaban.
- The 10 mg strength is a dark pink coloured film-coated tablet engraved with a ‘E842’ sign on one side. Each tablet contains 10 mg rivaroxaban.
- The 15 mg strength is a reddish-brown coloured film-coated tablet engraved with a ‘E843’ sign on one side. Each tablet contains 15 mg rivaroxaban
- The 20 mg strength is a brown coloured film-coated tablet engraved with a ‘E844’ sign on one side. Each tablet contains 20 mg rivaroxaban.

The film-coated tablets are packed in OPA/Al/PVC//Al blisters.

The excipients are:
Tablet core - microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, sodium laurilsulfate, magnesium stearate and colloidal anhydrous silica
Film-coating – hypromellose 3 cPs (E464), macrogol 3350 (E1521), talc (E553 b), titanium dioxide (E 171) and red iron oxide.

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or yellowish powder and practically insoluble in water. The drug substance used is the pure S-enantiomer and has polymorphic Form I as described in literature. In addition, the active substance is micronised.

The Active Substance Master File (ASMF) procedure is used for two manufacturers of 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.

The CEP procedure is used for one manufacturer of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

Manufacturer one - A CEP has been submitted; therefore no details on the manufacturing process have been included.

Manufacturer two - The synthesis of the active substance consists of two starting materials and involves four steps, yielding four isolated intermediates. In the fourth step, a third starting material is introduced. This step also includes purification of the crude rivaroxaban via crystallisation, recrystallisation, washing, and drying. The final synthetic step is followed by a fine milling process. The active substance is adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Manufacturer three – The synthesis involves two branches. In the first, an intermediate is made from a starting material in three steps. In the second, another intermediate is synthesised from two starting materials in three steps. These intermediates are then combined to form crude rivaroxaban, which is purified by crystallisation and drying. The active substance is adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is in line with the Ph. Eur. monograph, with additional requirements for polymorphic form and residual solvents. The specification is acceptable in view of the route of synthesis and various European guidelines and considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each supplier.

Stability of drug substance

Manufacturer one - The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Manufacturer two - Stability data on three batches have been provided stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). No clear trends or changes were observed in any of the tested parameters at both storage conditions. Photostability was demonstrated in line with ICH Q1B. The proposed retest period of 12 months without any special storage conditions is justified.

Manufacturer three - Stability data on several batches of rivaroxaban have been provided stored at 30°C/65% or 70% RH (up to 36 months) and 40°C/75% RH (6 months). No clear trends or changes were seen in any of the tested parameters at all three storage conditions. Photostability was demonstrated in line with ICH Q1B. Based on the presented stability data the proposed retest period of 3 years with storage conditions 'Store in closed, original containers, at temperature not above 30°C, transient spikes up to 40°C are permitted' is justified.

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 performed were the characterisation of the reference products, evaluation of critical attributes of the drug substance and excipients, formulation optimisation studies and manufacturing process optimization studies. It was demonstrated that the drug products can be administered through a nasogastric tube following the instructions in the SmPC in line with the reference products. Bioequivalence studies have been performed with the 10 mg and 20 mg products versus their respective reference product strengths. The batches used in these studies were manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at 3 pH's has been successfully studied in support of the biowaiver for the 2.5 mg and 15 mg products. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of wet granulation, blending, tabletting, film-coating and packaging and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches of the 2.5 mg

and 10 mg strengths. The 15 mg and 20 mg products are manufactured using conventional manufacturing techniques. Process validation for full-scale batches for these strengths will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements with additional acceptance limits for functionality-related characteristics. The film-coating materials are controlled according to in-house requirements. 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, identity, dimensions, average mass, uniformity of mass, disintegration time, resistance to crushing, water content, assay, uniformity of dosage units, dissolution, impurities and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four full-scale batches of 2.5 mg and 10 mg each and three full-scale batches and one pilot scaled batch of 15 mg and 20 mg each 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 (12-24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in OPA/Al/PVC-Al blisters. All parameters were in compliance with the shelf-life specification. 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 30 months with storage condition 'Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions' is justified.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Xiltess 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 Xiltess 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 pivotal bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test products Xiltess 10 mg and 20 mg film-coated tablets (Egis Pharmaceuticals Plc, Hungary) are compared with the pharmacokinetic profile of the reference products Xarelto 10 mg and 20 mg film-coated tablets (Bayer Pharma AG, Germany).

The choice of the reference product in the bioequivalence studies 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

The MAH requested a waiver for additional strength for rivaroxaban 2.5 and 15 mg tablets. The following conditions were 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 submitted
- The strengths are dose proportional.

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

Bioequivalence studies

Bioequivalence study I – single dose, 10 mg under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 26-60 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. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.5, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 15.00, 24.00, 36.00, and 48.00 after administration of the products.

The design of the study is acceptable. The procedures followed for a fasted study are in line with the bioequivalence guideline. The wash-out of 7 days is long enough to prevent carry-over effects, as this is more than five times the half-life ($t_{1/2}$= ~10 hours). In addition, multiple blood samples were drawn around the expected t_{max} (~3 h post dose) and sampling scheme is adequate to estimate pharmacokinetic parameters.

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

One subject tested positive for cannabis and one subject tested positive for IGG and IGM antibodies. Therefore, 34 subjects completed the study were eligible for pharmacokinetic analysis.

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

Treatment N=32	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)

Test	1365.6 ± 387.4	1425.0 ± 379.7	167.9 ± 47.1	2.5 (0.5-4.5)
Reference	1441.7 ± 397.8	1505.7 ± 390.3	189.0 ± 58.4	2.0 (1.0-5.0)
***Ratio (90% CI)**	0.94 (0.90 – 0.99)	--	0.89 (0.84 – 0.95)	--
$AUC_{0-\infty}$ 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*

Bioequivalence study II – single dose, 20 mg under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male and female subjects, aged 24-60 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 a standardised, high-fat, high-calorie meal (consisting of milk, eggs, hash brown potatoes, toast, butter and bacon). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.5, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 15.00, 24.00, 36.00, and 48.00 after administration of the products.

The design of the study is acceptable. The procedures followed for a fed study are in line with the bioequivalence guideline and composition of the high-fat, high-calorie meal is considered acceptable. The wash-out of 7 days is long enough to prevent carry-over effects as this is more than 5 times the half-life ($t_{1/2}$= ~10 hours). In addition, multiple blood samples were drawn around the expected t_{max} (~3 h post dose) and sampling scheme is adequate to estimate pharmacokinetic parameters.

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 32 subjects completed the study were eligible for pharmacokinetic analysis.

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

Treatment N=32	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)

Test	3198.1 ± 783.6	3240.5 ± 789.0	379.0 ± 84.7	4.5 (1.0 -8.0)
Reference	3078.8 ± 727.3	3131.0 ± 736.9	384.0 ± 79.6	4.0 (0.75-8.0)
***Ratio (90% CI)**	1.04 (1.01 – 1.07)	1.03 (1.00 – 1.06)	0.99 (0.92 – 1.06)	--
$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Xiltess is considered bioequivalent with Xarelto.

The MEB has been assured that the bioequivalence studies have 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 Xiltess.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal 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)

At the time of approval of this product, it was considered that additional risk minimisation measures (including educational material) were necessary for the safe and effective use of the product. The educational material should be submitted by the MAH to the competent authorities of the Member States and its content and implementation should be agreed with the competent authorities prior to launch.

The educational material should contain the following key elements:

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use rivaroxaban. 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 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 MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in the product 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 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

The package leaflet (PL) 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 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xiltess 2.5 mg, 10 mg, 15 mg and 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 Xiltess with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 November 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
NL/H/5431/ 1-4/IB/001	B.II.b.5.a: Change to in-process tests or limits applied during the manufacture of the finished product; tightening of in-process limits	No	17-05-2023	Approved	NA
NL/H/5431/ 1-4/IB/002	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 is required to be submitted by the MAH	Yes	08-08-2023	Approved	NA
NL/H/5431/IB/003/G	- B.I.a.1.z: Addition of new intermediate manufacturing site -B.I.a.1.a: Addition of new starting material manufacturing site - A.7: Deletion of intermediate and starting material manufacturing site - B.I.b.2.a: Minor changes to the approved test procedure (DMSO)	No	13-10-2023	Approved	NA
NL/H/5431/ 1-4/IA/004	C.I.3.a: Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; Implementation of wording agreed by the competent authority	Yes	10-10-2023	Approved	NA
NL/H/5431/ 1-4/IA/005	B.I.a.3.a: Change in batch size (including batch size ranges) of active substance or intermediate used in the	No	01-02-2024	Approved	NA

	manufacturing process of the active substance; up to 10-fold increase compared to the manufacturing process of the active substance				
NL/H/5431/002/IA/006	B.II.b.4.a: Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size	No	22-03-2024	Approved	NA
NL/H/5431/IA/007/G	B.I.a.4.b: Mechanical impurity tests are introduced B.I.a.4.a: Tightening of in-process limit B.I.a.3.a: Alternative increasement in batch size used for manufacture of rivaroxaban drug substrate	No	10-04-2024	Approved	NA