18 September 2025
EMA/335639/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rivaroxaban Koanaa

International non-proprietary name: rivaroxaban

Procedure No. EMEA/H/C/006643/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACS	acute coronary syndrome
AE	adverse event
Alu	aluminium
ANOVA	analysis of variance
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AUC	the area under the plasma concentration
AUC_{0-t}	area under the plasma concentration - time curve from time 0 to T hours
$AUC_{0-\infty}$	area under the plasma concentration - time curve from time 0 to infinity
BE	bioequivalence
BMI	body mass index
CAD	coronary artery disease
CEP	Certificate of Suitability of the European Pharmacopoeia
CHMP	the Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum plasma concentration
CoA	certificate of analysis
CQA	critical quality attribute
CRF	case report form
CV	coefficient of variation
DIQC	dilution integrity quality control
DVT	deep vein thrombosis
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU/EEA	European Union/European economic area
FMEA	failure mode effects analysis
GCP	good clinical practice
GLM	general linear model
GMP	good manufacturing practice

h/hrs	hour/hours
HQC	high quality control
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICD	informed consent document
IUPAC	International Union of Pure and Applied Chemistry
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
Ln	logarithmic value to the base "*e*"
LoQ	list of questions
LQC	low quality control
LSM	least square mean
MO	major objection
MQC	medium quality control
NDSRIs	nitrosamine drug substance-related impurities
OC	other concern
ODF	orodispersible film
ODT	orodispersible tablet
PAD	peripheral artery disease
PD	pharmacodynamic
PE	pulmonary embolism
PE	polyethylene
PEC_{sw}	predicted environmental concentration in surface water
PET	polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PI	principal investigator
PK	pharmacokinetic
pKa	acid dissociation constant
POM	prescription only medicine
PRAC	Pharmacovigilance Risk Assessment Committee
PSD	particle size distribution
PT	prothrombin time
QbD	quality by design
QC	quality control

q.s.	*quantum satis,* a sufficient quantity
QTPP	quality target product profile
R	reference product
RPM	rotation per minute
SAS	statistical analysis system
SGPT	serum glutamate pyruvate transaminase
SLS	sodium lauryl sulfate
SmPC	summary of product characteristics
SOP	standard operating procedure
T	test product
T_{max}	time of the maximum measured plasma concentration
$T_{1/2}$	the elimination or terminal half-life
λ z	first order rate constant associated with the terminal portion of the curve
USP	United States Pharmacopoeia
UV	ultraviolet
VTE	venous thromboembolism
Vss	volume of distribution, steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Koanaa Healthcare Spain S.L. submitted on 8 October 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Rivaroxaban Koanaa, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2024.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

- **Rivaroxaban Koanaa 2.5 mg**

  Rivaroxaban Koanaa, 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 (see sections 4.3, 4.4 and 5.1).

  Rivaroxaban Koanaa, 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.

- **Rivaroxaban Koanaa 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. (See section 4.4 for haemodynamically unstable PE patients).

- **Rivaroxaban Koanaa 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. (See 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.

- **Rivaroxaban Koanaa 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. (See 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xarelto instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Xarelto 2.5, 10, 15 and 20 mg film coated tablets
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 30-09-2008
- Marketing authorisation granted by: Union
- Union Marketing authorisation number: EU/1/08/472

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xarelto 2.5, 10, 15 and 20 mg film coated tablets
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 30-09-2008
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/472

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xarelto 2.5, 10, 15 and 20 mg film coated tablets
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 30-09-2008
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/08/472

- Bioavailability study numbers: Study 097/22 and Study 013/24

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Daniela Philadelphy

The application was received by the EMA on	8 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 January 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	14 August 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint	02 September 2025

Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rivaroxaban Koanaa on	18 September 2025

2. Scientific discussion

2.1. Introduction

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi (or blood cloths). Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated. The reference product is Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets, marketed by Bayer AG, Germany. Xarelto was first approved in Europe in 2008.

This centralised marketing authorisation application concerns Rivaroxaban Koanna 10 mg, 15 mg and 20 mg orodispersible films, a generic version of rivaroxaban. Koanaa Healthcare Spain S.L. submitted an abridged application relying on the clinical data of the reference product. Essential similarity between the test product and the EU reference product was established.

in vivo for strengths 10 mg and 20 mg providing results of 2 bioequivalence studies (Study 097/22 and Study 013/24) and *in vitro* for the strength 15 mg. A biowaiver for this strength has been requested by the applicant based on the satisfactory bioequivalence study on 20 mg strength (study 013/24) and *in vitro* dissolution data comparison.

Initially, authorisation of a 2.5 mg strength was requested but was removed during the assessment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as orodispersible films containing 10 mg, 15 mg, and 20 mg of rivaroxaban as active substance.

Other ingredients are: microcrystalline cellulose, hypromellose, povidone, macrogolglycerol hydroxystearate, sodium lauryl sulfate, sucralose, maltodextrin, red iron oxide, peppermint flavour, triethyl citrate, glycerol.

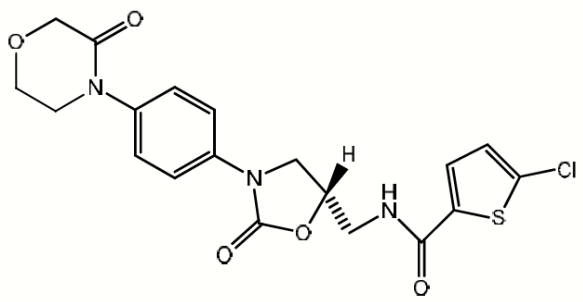
The product is available in 4 ply laminate pack (i.e. paper/PET/Alu/PE-sachet) as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of rivaroxaban is 5-Chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide corresponding to the molecular formula $C_{19}H_{18}ClN_3O_5S$. It has a molecular weight of 435.88 and the following structure:

Figure 1. Active substance structure



The active substance is a white or yellowish powder, practically insoluble in water (and over the physiological pH range), freely soluble in dimethyl sulphoxide. It classifies as BSC class II (low soluble, highly permeable).

Adequate information is given on physical characteristics of the active substance such as solubility, pKa, partition coefficient, hygroscopicity, melting point, isomerism and polymorphism. Rivaroxaban exhibits isomerism as it has one chiral centre at oxazolidine group of the molecule.

As there is a monograph of rivaroxaban in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for rivaroxaban which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

One active substance manufacturer is proposed. The relevant information has been assessed by the EDQM before issuing the CEP. The active substance is micronised to meet the required particle size. A description of the micronisation process, performed by the active substance manufacturer, is provided in the module 3.

As stated in the CEP, rivaroxaban is packed double polyethylene bags (outer black) placed in polyethylene container.

Specification

An active substance specification, in compliance with the Ph. Eur. and USP monograph, is provided by the finished product manufacturer and it is shown in Table 1. It includes tests for description (Ph. Eur.), solubility (Ph. Eur.), identification test (Ph. Eur.: IR, HPLC), water content (Ph. Eur., coulometry), sulfated ash (Ph. Eur.), assay (Ph. Eur.: HPLC), related substances (HPLC), impurity A and enantiomeric purity (Ph. Eur.: HPLC). Particle size distribution (Ph. Eur. by Malvern), X-ray diffractometry (Ph. Eur.), microbial limit tests (Ph. Eur.) are included as additional parameters. Residual solvents content HPLC) is included as per the CEP.

All additional methods have been adequately validated and described according to ICH Q2. The PSD limit is justified based on the active substance batches, which have been used to manufacture the test batch of the ODF for the BE studies.

Batch analysis data on commercial-scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. As the active substance is supported by CEP, this is considered acceptable.

Stability

No retest period is stated in the CEP. Stability data from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. All tested parameters were within the specifications.

The applicant confirms that they will test the micronised active substance prior to use, in accordance with the release specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when packed in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as orodispersible films (ODF) containing 10 mg, 15 mg, and 20 mg of rivaroxaban active substance. The light red rectangular-shaped, orally dissolving thin films are packed in a 4-ply laminate pouch (paper/PET/Al/peelable PE).

All excipients are well known pharmaceutical ingredients, and their quality, or the quality of their components, is compliant with Ph. Eur. standards, with the exception of peppermint flavour, which is of food grade. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Pharmaceutical development of the finished product contains quality by design (QbD) elements.

The quality target product profile (QTPP) was defined as an immediate release oral dosage form and was based on the properties of the active substance, characterisation of the reference product, including its label claim and intended patient population. An orodispersible film (ODF) formulation was chosen. The excipients were selected based on previous experience on ODF formulation development and based on literature. Compatibility studies concluded that there is no potential interaction between the active substance rivaroxaban and selected excipients for the proposed formulation.

Identification of critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet the quality attribute of the finished product. The CQAs identified were: assay, content uniformity, dissolution, related substances, taste, identification, microbial limit. A major objection (MO) was raised by the CHMP requesting that the development of

orodispersible films should include the investigation of various mechanical/physical properties to ensure the integrity of the films. These attributes and their control were discussed in detail and included in the specification of the finished product. Batch data were provided to justify the specification limits. The MO was considered as adequately addressed.

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical material attributes (active substance and excipients), process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical material attributes and process parameters have been adequately identified.

Although the applicant has applied QbD principles in the development of the finished product and their manufacturing process, no design spaces were claimed for the manufacturing process of the finished product.

During the dissolution method development, different apparatus and different dissolution media (were used. In each medium, surfactant was applied. The concentration of the surfactant is sufficiently justified by solubility data. The final QC dissolution method is considered adequate, and its discriminatory power has been demonstrated. During the procedure an MO (MO2) was raised with regards to the dissolution method to clarify four main aspects: 1. the strength used during the development of the dissolution method; 2. the dissolution behaviour of the active substance 3. setting the specification limits based on the bio batches data; 4. demonstration of the discriminatory power at the proposed specification limit. The MO was considered resolved as the source of the data was clarified; the applicant confirmed that rivaroxaban is not stable in the proposed media, and the specification limit was tightened in line with the bio batches data and also supporting the discriminatory power of the method.

The formulation used during the bioequivalence clinical studies is the same as that intended for marketing. Bioequivalence study was performed showing bioequivalence between the reference product (film coated tablets) and the proposed product (ODF).

The primary packaging is a 4-ply laminate pack (i.e. paper/PET/Alu/PE-sachet). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

For each strength, the size and thickness of the films are provided. Different colours are used to differentiate the strengths of the primary and secondary packaging. The packaging size is also different for the three strengths; hence the differentiation is considered adequate.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturer During the procedure; a MO was raised requesting proof of GMP compliance for the manufacturer. In response, a valid GMP certificate was provided to resolve this MO.

The manufacturing process consists of four main steps. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by several studies.

During the procedure, a MO was raised related to the acceptability of the proposed batch size in relation to the mechanical/physical properties of each strength. In response, the applicant demonstrated that the mechanical/physical properties of the orodispersible films are consistent irrespective of the size/strength of films; hence, the manufacturing of the ODFs is considered not to be susceptible to scale-up effects and full-scale validation data was no longer considered needed pre-approval.

It has been demonstrated that the manufacturing process can produce the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description (visual), identification (HPLC, PDA and UV detector), water content (Ph. Eur. KF), assay (HPLC), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), microbial limit (Ph. Eur.), water activity (Ph. Eur.), tensile strength (in-house), folding endurance (in-house), disintegration time (ph. Eur.) and average mass (Ph. Eur.).

The specification complies with Ph. Eur. monograph 'Pharmaceutical Preparations' and ICH Q6A, which is considered adequate. There are no specified impurities.

During the procedure, as discussed under the pharmaceutical development section, specification tests related to the physico-chemical characteristics of the ODF pharmaceutical form have been included in the finished product specification. Specification limits for visual description, dissolution, tensile strength have been updated and reference to Ph. Eur. included as applicable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

During the procedure a MO was raised in relation to nitrosamine impurities. The applicant provided data demonstrating no potential nitrosamine impurities were detected over the proposed shelf-life. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Stability of the product

Stability data commercial-scale batches of finished product stored for up to 18 months under long term conditions 12 months under intermediate conditions, and for up to 6 months under accelerated conditions according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The conditions tested are the same as for release except for the omission of identification by PDA and uniformity of dosage units; since these parameters are non-stability indicating, their omission is acceptable. The results obtained for all parameters are within the specification limits. As there are no significant changes in tested parameters at accelerated conditions, no temperature storage restriction is proposed in the product information.

In addition, a forced degradation study was carried out as part of the analytical method validation to prove the specificity of the HPLC method for assay of Rivaroxaban Orodispersible films. The following forced degradation studies were conducted: 1. acid degradation, 2. alkali degradation, 3. oxidation degradation, 4. thermal degradation, 5. humidity and 6. photo stability.

One batch per strength of the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on the results of photostability study, it is concluded that the product is not light sensitive.

Based on available stability data, the proposed shelf-life of 18 months with no storage conditions, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

During the procedure 5 MOs were raised and these were satisfactorily resolved.

MO1 requested that the development of orodispersible films included the investigation of various mechanical/physical properties to ensure the integrity of the films. MO2 requested clarification on the source of the data, tightening of the QC dissolution test specification limit and demonstration of its discriminatory power. The MO was considered resolved as the source of the data was clarified and the specification limit was tightened, in line with the bio batches data and also supporting the discriminatory power of the methodMO3, related to the GMP compliance for an additional quality control testing site was resolved by providing a valid certificate.

MO4, related to the susceptibility of the CQAs to scale-up, was resolved by providing adequate justification MO5, related to the potential presence of nitrosamine impurities was resolved by the provision of data confirming that no potential nitrosamine impurities were detected over the proposed shelf-life. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant provided an ERA consisting of a Phase I as well as a limited Phase II risk assessment.

In Phase I, a PECsw calculation was performed based on refined Fpen values derived from consumption data in European countries of the last three years. The resulting PECsw was 0.115 µg/L and, thus, exceeds the action limit of 0.01µg/L. Therefore, the ERA entered a Phase II assessment. The data submitted originates from a publicly available source and comprise results of the following aquatic toxicity studies: Algae growth inhibition test OECD 201 with *Desmodesmus subspicatus*, Daphnia magna reproduction test OECD 202 and fish early life stage toxicity test OECD 210. The NOEC obtained for the fish study was used as a basis for the PNEC calculation). The resulting risk quotient for rivaroxaban is < 1.

In addition, the result of a respiration inhibition test in activated sludge OECD 209 was provided. Ready biodegradability was evaluated by OECD test 301F. To follow up the low biodegradability of rivaroxaban the aerobic and anaerobic transformation in aquatic sediment systems test OECD 308 was provided.

Table 1. Summary of main study results

Substance (INN/Invented Name): Rivaroxaban			
CAS-number (if available):			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence,	0.115	µg/L	> 0.01 threshold (Y)

literature)			
Other concerns (e.g. chemical class)			(N)

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is of low quality but considered sufficient.

Environmental Risk Assessment

The provided ERA data are considered sufficient to conclude that rivaroxaban does not have a potential environmental risk.

2.3.4. Conclusion on the non-clinical aspects

It is considered that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is of low quality, but no follow-up question is raised.

There are no objections to approval of Rivaroxaban Koanaa from a non-clinical point of view.

ERA

All issues have been sufficiently addressed.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for orodispersible films containing rivaroxaban. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting or fed conditions. These studies were pivotal for the assessment.

No formal scientific advice by the CHMP was given for this medicinal product.

For the clinical assessment Guideline on the *Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/ Corr*** (BE guideline, 20 January 2010) as well as the Guideline on *Bioanalytical method validation EMEA/CHMP/EWP/192217/09, Rev.1 Corr. 2*** (21 July 2011) are of particular relevance. The guidance *Rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg product-specific bioequivalence guidance EMA/CHMP/160650/2016* (1 April 2016) was also of relevance.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of rivaroxaban based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant requested a biowaiver for the 15 mg orodispersible films.

Conditions for a waiver for additional strength(s), as outlined in the BE guideline, are fulfilled:

1. All three strengths of Rivaroxaban 10 mg, 15 mg and 20 mg Orodispersible films are manufactured by the same manufacturer and using the same manufacturing process.

2. The composition of Rivaroxaban 10 mg, 15 mg and 20mg Orodispersible films are dose proportional to BE strength, Rivaroxaban 10 mg and 20mg Orodispersible films where the concentrations of excipients are same & the API. According to the composition table, the ingredients of all strengths are qualitatively the same, excluding colour agents.

3. The pharmacokinetics of rivaroxaban are approximately linear up to about 15 mg, while in doses above less than a proportional increase in exposure was noted after a single dose. The BE Guideline specifies that for drugs with non-linear pharmacokinetics characterised by less than a proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength. This approach was selected and applies for the extrapolation to the 15 mg strength, which is bracketed by the BE studies with 10 mg (study 097-22) and 20 mg (study 013-24) strength, taking into the account the food recommendations in the reference product's SmPC and recommendation of the product-specific bioequivalence guidance for rivaroxaban film-coated tablets.

The overview indicates that dissolution studies were performed on Rivaroxaban Test 20 mg ODF versus Rivaroxaban Test 15 mg ODF, and the obtained dissolution values were found to be acceptable. The f_2 criteria were met for all media except in 6.8 phosphate buffer, where the dissolution method comparison was conducted using the bootstrap approach and demonstrated similarity.

Tabular overview of clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

Table 2. Tabular overview of clinical studies

Project	Rivaroxaban Orodispersible Film 10 mg	Rivaroxaban Orodispersible Film 20 mg
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of Rivaroxaban Orodispersible Film 10 mg (Test) of Shilpa Medicare Limited, India and Xarelto (Rivaroxaban) 10 mg film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fasting conditions.	An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of Rivaroxaban Orodispersible Film 20 mg (Test) of Shilpa Medicare Limited, India and Xarelto 20 mg (Rivaroxaban) film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fed conditions.
Study Code	097-22	013-24

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 097/22 : An open label, balanced, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of Rivaroxaban Orodispersible Film 10 mg (Test) of Shilpa Medicare Limited, India and Xarelto (Rivaroxaban) 10 mg film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fasting conditions.

Methods

- **Study design**

The study is designed as an open label, balanced, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fasting conditions, investigating the bioequivalence of rivaroxaban Koanaa 10 mg orodispersible films to Xarelto 10 mg film-coated tablets of Bayer AG.

This was an open-label study. However, the Bio-analytical facility was blinded to the randomisation code to prevent bias during analysis.

Administration of Reference product (R):

After an overnight fast of at least 10.00 hours, subjects were dosed with a single oral dose of reference product (Xarelto 10 mg film-coated tablets (Rivaroxaban)) × 1 Tablet of Reference product (R) with approximately 240 mL of drinking water at room temperature as per randomisation schedule.

Administration of Test product (T):

After an overnight fast of at least 10.00 hours, prior to drug administration, each subject was instructed to wet his mouth with approximately 20 mL of water and subjects were dosed with a single oral dose Rivaroxaban Orodispersible Film 10 mg × 1 Film of Test product (T) was placed on the subjects' tongue in sitting posture and it was allowed to disintegrate completely. After disintegration, subjects were asked to swallow the content of product without drinking water.

Oral Irritation assessment was performed for subjects receiving Test product at 01.00 and 03.00 hours after dosing, with a window period of ± 20 minutes. Oral Irritation assessment was performed in the presence of Investigator. Subjects were asked about palatability & swallowability of Test product.

Protocol number: 097-22

Date of final protocol: 05 February 2024 (Version 02)

Date of report: 02 August 2024 (Version 01)

Clinical Study Dates

Study initiation date: 20 April 2024 (ICD initiation date)

Study completion date: 05 Mai 2024 (last blood sample collection of the study)

Table 3. Duration of the clinical study

	Start date	End date
Period 01	22/04/24	25/04/24
Washout	10 days	
Period 02	02/05/24	05/05/24

Total duration of the clinical study was 14 days.

Bioanalytical Study Dates

30 May to 18 June 2024

A single pre-dose blood sample of 10 mL was collected in each period. The post-dose blood samples of 5 mL each were drawn at 00.17, 00.33, 00.50, 00.75, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours in each period.

- **Test and reference products**

Rivaroxaban ODF manufactured by Shilpa Medicare (Batch number 424S001C, manufacturing date 01/2024) has been compared against Xarelto 10 mg tablets (batch number BT164N1, expiry date 07/2024)

- **Population studied**

Male volunteers aged from 23-42 years with a body mass index (BMI) in the range of 19.32-29.77 kg/m^2 were selected according to the inclusion and exclusion criteria. They were assessed to be in healthy condition judged by the PI based on screening within 28 days prior to study check-in and pre-study medical examination and laboratory tests. Based on the expected maximum intra-subject variability a sample size of 44 subjects were required.

- **Analytical methods**

Study No. 097-22

The analytical part of the study lasted from 30.05.2024. till 05.05.2024 (Rivaroxaban); study samples were stored at a nominal temperature of -70ºC.

2088 samples from 48 subjects (22 time-points per subject, 2 periods) were analysed, the theoretical number of samples is 2116*.

**Indicates number of samples as per Clinical Protocol were 2116 (i.e., total 48 subjects with two periods, each period has 22 time points and pre-dose samples of 4 standby subjects, i.e., 48x2x22+4 = 2116). According to the clinical protocol (097-22) section No. 8.3, 04 standby subjects will be recruited in order to dose 48 subjects so, 04 standby subjects were taken into the consideration for the Number of Samples as per Clinical Protocol calculation.*

Analytical Methods

The analyte is Rivaroxaban.

As regards Rivaroxaban, internal standard was Rivaroxaban D4; samples were extracted from a 0.010 mL aliquot of K2EDTA human plasma by liquid-phase extraction. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted (1/c2) linear regression is performed to determine the concentration of the analytes.

The validated calibration range for the assay of Rivaroxaban is from 1.001 ng/mL to 601.997 ng/mL.

Long term matrix stability

The Long-term matrix stability was evaluated using low, high and dilution integrity QC samples (LQC, HQC & DIQC) processed and analysed along with freshly prepared calibration curve standards and six sets of performance QC samples.

The % CV at LQC, MQC, HQC & DIQC for comparison samples was found to be 2.02%, 1.29%, 0.88% and 1.72% respectively.

The % mean accuracy at LQC, MQC, HQC & DIQC for comparison samples was found to be 101.05%, 100.56%, 102.58% and 101.89%.

Long term matrix stability at -70 ± 15°C

The Long-term stability at -70 ± 15°C was proved for 136 days to that of comparison samples.

The % CV at LQC, HQC and DIQC was found to be 1.53%, 0.61% and 0.7% respectively. The % mean stability was found to be 91.87% for LQC, 91.42% for HQC and 93.01% for DIQC.

Long term matrix stability at -20 ± 5°C

The Long-term stability at -20 ± 5°C was proved for 136 to that of comparison samples.

The % CV at LQC, HQC and DIQC was found to be 8.88%, 2.30% and 2.51% respectively. The % mean stability was found to be 95.47% for LQC, 88.81% for HQC and 90.16% for DIQC.

Observations and comments

Sample re-assays for Rivaroxaban were done on 1 samples (0.05%). All re-assays are in accordance with the presented SOP and the relevant guideline.

Incurred sample re-analysis (ISR) of Rivaroxaban has been performed on about 6 samples for each subject and study period (~ 10% of total samples analysed); 202 out of 202 ISR samples (100%) were within 20% from the mean value.

Representative chromatograms (subjects 1-48, ~100%) were provided.

- **Pharmacokinetic variables**

Primary Pharmacokinetic parameters: AUC_{0-t}, C_{max}

Further Pharmacokinetic parameters: $AUC_{0-\infty}$, T_{max}, Residual area, λ_Z and T½

Calculation of pharmacokinetic parameters was done for Rivaroxaban using drug concentration time data by non-compartmental method using SAS® Release 9.4 (SAS Institute Inc., USA).

- **Statistical methods**

Summary statistics, ANOVA, 90% confidence interval, ratio analysis, intra subject variability and power were calculated for Rivaroxaban. Geometric means and ratio of means were calculated for Rivaroxaban. ANOVA was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Rivaroxaban.

Test product (T) would be considered as bioequivalent to the Reference product (R) if the 90% CI (confidence interval) for geometric least square mean ratios of Ln-transformed parameters C_{max} and AUC_{0-t} of Rivaroxaban falls within the acceptance range of 80.00% - 125.00%.

The factors included in the model, the treatment received, the period at which it is given along with the sequence in which each treatment being received and the subject effect (nested within the sequence). Fixed effects were used for all factors included in ANOVA model. Each analysis of variance was included in the calculation of least square mean (LSM).

All statistical analyses for Rivaroxaban were performed using PROC GLM of SAS® Release 9.4 (SAS Institute Inc., USA).

Results

Of the 48 subjects enrolled and randomised, 47 completed the clinical phase (completed both periods). Subject 20 was withdrawn due to rash in period I. 47 subjects were included in the statistical analysis.

Table 4. Pharmacokinetic parameters for rivaroxaban (non-transformed values, n=47)

Pharmacokinetic parameter		Test		Reference	
		arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	(ng/ml/h)	1374.76	336.502	1347.46	280.685
$AUC_{(0-\infty)}$	(ng/ml/h)	1410.32	325.226	1381.90	280.559
C_{max}	(ng/ml)	202.03	57.022	200.51	48.029
T_{max}*	(h)	2.00	0.75-4.50	2.00	0.75-4.50
$t_{1/2}$	(h)	6.53	2.282	6.96	2.106
AUC_{0-t}	*area under the plasma concentration-time curve from time zero to t hours*				
$AUC_{0-\infty}$	*area under the plasma concentration-time curve from time zero to infinity*				
C_{max}	*maximum plasma concentration*				
T_{max}	*time for maximum concentration (* median, range)*				
$t_{1/2}$	*half-life*				

Table 5 Statistical analysis for rivaroxaban (ln-transformed values, n=47)

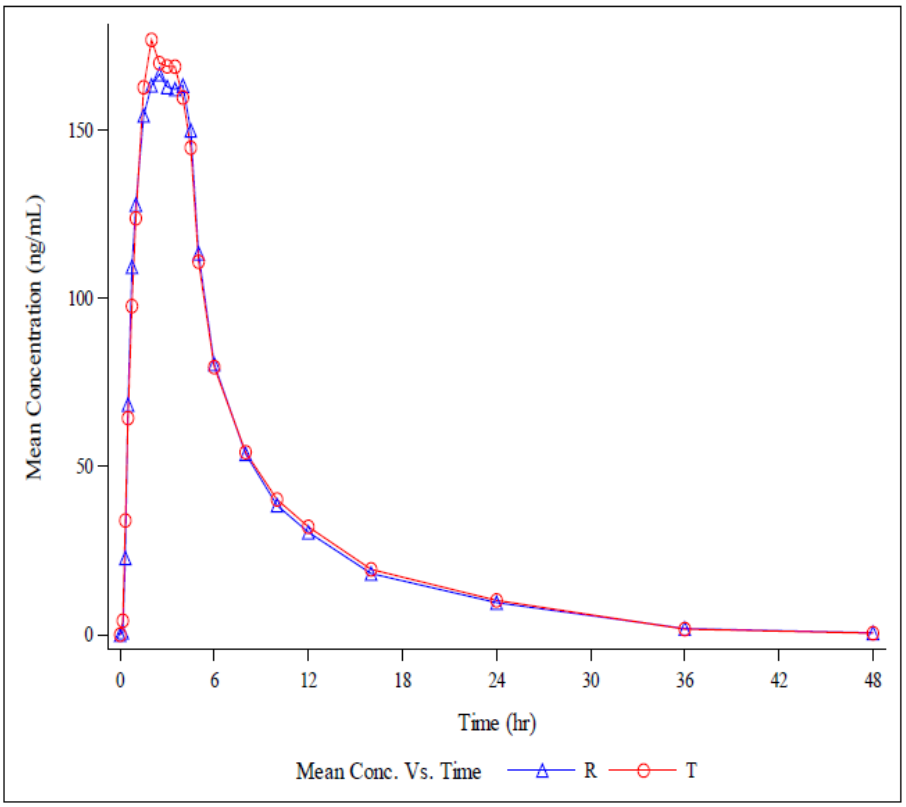
Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$	101.42	95.57-107.63	17.28

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
C_{max}	99.64	92.59-107.24	21.43
**Estimated from the Residual Mean Squares*			

The 90% confidence intervals for geometric least square mean ratios of Ln-transformed parameters C_{max} and AUC_{0-t} of Rivaroxaban were within the bioequivalence acceptance range of 80.00%-125.00%.

Based on the study results, Rivaroxaban Orodispersible Film 10 mg (Test) of Shilpa Medicare Limited, India is bioequivalent to Xarelto (Rivaroxaban) 10 mg film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fasting conditions.

Figure 2. Linear plot of mean plasma concentrations vs time profile of Rivaroxaban under fasting conditions



For C_{max} and AUC_{0-t}:

Sequence, period and treatment effects for ln-transformed data were found to be statistically insignificant at 5% level of significance.

Subject (Sequence) effect for ln-transformed data was found to be statistically significant at 5% level of significance. The Subject (Sequence) effect in a bioequivalence study indicates an unequal carryover effect. However, in the present study a true carryover effect is not visible as there are no pre-dose concentrations (> 5% of C_{max}) in period II, of any of the subjects.

- **Safety data**

One adverse event was reported in one subject during period-I (R): rash (moderate). This subject was treated with cetirizine 10mg oral. No adverse events were reported during washout period and period-II and post study. Overall, Rivaroxaban Orodispersible Film 10 mg were well tolerated as a single oral dose of 1 x 10 mg when administered under fasting conditions.

Based on evaluation of adverse events, clinical laboratory evaluation and vital signs examination, it was concluded that both the Test product (T) and Reference product (R) were well tolerated and found to be safe.

Study 013/24 : An open label, balanced, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study of Rivaroxaban Orodispersible Film 20 mg (Test) of Shilpa Medicare Limited, India and Xarelto (Rivaroxaban) 20 mg film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fed conditions.

Methods

- **Study design**

The study is designed as an open label, balanced, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fed conditions, investigating the bioequivalence Rivaroxaban Koanaa 20 mg orodispersible films to Xarelto 20 mg film-coated tablets of Bayer AG.

This was an open-label study. However, the Bio-analytical facility was blinded to the randomisation code to prevent bias during analysis.

Administration of Reference product (R):

After an overnight fast of at least 10.00 hours and exactly 30 minutes after serving of high fat, high calorie breakfast, subjects were dosed with a single oral dose of reference product (Xarelto 20 mg a film-coated tablets (Rivaroxaban)) × 1 Tablet of Reference product (R) with approximately 240 mL of drinking water at room temperature as per randomisation schedule.

Administration of Test product (T):

After an overnight fast of at least 10.00 hours and exactly 30 minutes after serving of high fat, high calorie breakfast, prior to drug administration, each subject was instructed to wet his mouth with approximately 20 mL of water and subjects were dosed with a single oral dose Rivaroxaban Orodispersible Film 20 mg × 1 Film of Test product (T) was placed on the subjects tongue in sitting posture and it was allowed to disintegrate completely. After disintegration, subjects were asked to swallow the content of product without drinking water.

Oral Irritation assessment was performed for subjects receiving Test product at 01.00 and 03.00 hours after dosing, with a window period of ± 20 minutes. Oral Irritation assessment was performed in the presence of Investigator. Subjects were asked about palatability & swallowability of Test product.

Meals

Subjects were instructed to be required to fast overnight for at least 10.00 hours before serving of high fat, high calorie breakfast (before dosing) and a minimum of 04.00 hours after dosing. The high fat, high calorie breakfast contained 966.88 kcal (26.80% carbohydrates, 15.77% protein and 57.42% fat).

Protocol number: 013-24

Date of final protocol: 18 January 2024 (Version 01)

Date of report: 02 August 2024 (Version 01)

Clinical Study Dates

Study initiation date: 22 March 2024 (ICD initiation date)

Study completion date: 05 April 2024 (last blood sample collection of the study)

Table 6. Duration of the clinical study

	Start date	End date
Period 01	25/03/24	28/03/24
Washout	08 days	
Period 02	02/04/24	05/04/24

Total duration of the clinical study was 12 days.

Bioanalytical Study Dates

24 April to 30 May 2024

A single pre-dose blood sample of 10 mL was collected in each period. The post-dose blood samples of 5 mL each were drawn at 00.25, 00.50, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 14.00, 16.00, 20.00, 24.00, 36.00 and 48.00 hours in each period.

- **Test and reference**

Rivaroxaban ODF manufactured by Shilpa Medicare (Batch number 424S001A, manufacturing date 01/2024) has been compared against Xarelto 20 mg tablets (batch number BT18AF1, expiry date 01/2026).

- **Population studied**

Male volunteers aged from 21-42 years with a body mass index (BMI) in the range of 18.78-29.90 kg/m^2 were selected according to the inclusion and exclusion criteria. They were assessed to be in healthy condition judged by the PI based on screening within 28 days prior to study check-in and pre-study medical examination and laboratory tests. Based on the expected maximum intra-subject variability a sample size of 42 subjects were required.

- **Analytical methods**

Study No: 013-24

The analytical part of the study lasted from 24.04.2024 till 30.05.2024 (Rivaroxaban); study samples were stored at a nominal temperature of -70ºC.

2219 samples from 48 subjects (24 time-points per subject, 2 periods) were analysed, the theoretical number of samples is 2308 (the total number of samples including 4 standby subjects pre-dose

samples; 48*2*24=2304, 4 standby subject samples pre-dose samples, total number of samples as per clinical protocol are 2308).

Analytical Methods
The analyte is Rivaroxaban.

As regards Rivaroxaban, internal standard was Rivaroxaban D4; samples were extracted from a 0.010 mL aliquot of K2EDTA human plasma by liquid-phase extraction. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted (1/c2) linear regression is performed to determine the concentration of the analytes.

The validated calibration range for the assay of Rivaroxaban is from 1.001 ng/mL to 601.997 ng/mL.

Long term matrix stability

The Long-term matrix stability was evaluated using low, high and dilution integrity QC samples (LQC, HQC & DIQC) processed and analysed along with freshly prepared calibration curve standards and six sets of performance QC samples.

The % CV at LQC, MQC, HQC & DIQC for comparison samples was found to be 2.02%, 1.29%, 0.88% and 1.72% respectively. The % mean accuracy at LQC, MQC, HQC & DIQC for comparison samples was found to be 101.05%, 100.56%, 102.58% and 101.89%.

Long term matrix stability at -70 ± 15°C

The Long-term stability at -70 ± 15°C was proved for 136 days to that of comparison samples.

The % CV at LQC, HQC and DIQC was found to be 1.53%, 0.61% and 0.7% respectively. The % mean stability was found to be 91.87% for LQC, 91.42% for HQC and 93.01% for DIQC.

Long term matrix stability at -20 ± 5°C

The Long-term stability at -20 ± 5°C was proved for 136 to that of comparison samples.

The % CV at LQC, HQC and DIQC was found to be 8.88%, 2.30% and 2.51% respectively. The % mean stability was found to be 95.47% for LQC, 88.81% for HQC and 90.16% for DIQC.

Observations and comments

Sample re-assays for Rivaroxaban were done on 291 samples (8.11%). All re-assays are in accordance with the presented SOP and the relevant guideline.

Incurred sample re-analysis (ISR) of Rivaroxaban has been performed on about 6 samples for each subject and study period (~ 10% of total samples analysed); 224 out of 225 ISR samples (~99.6%) were within 20% from the mean value.

Representative chromatograms (subjects 1-48, ~100%) were provided.

- **Pharmacokinetic Variables**

Primary Pharmacokinetic parameters: AUC_{0-t}, C_{max}

Further Pharmacokinetic parameters: $AUC_{0-\infty}$, T_{max}, Residual area, λ_Z and T½

Calculation of pharmacokinetic parameters was done for Rivaroxaban using drug concentration time data by non-compartmental method using SAS® Release 9.4 (SAS Institute Inc., USA).

- **Statistical methods**

Pharmacokinetic parameters were determined from the plasma Rivaroxaban concentration data by using SAS® Release 9.4 (SAS Institute Inc., USA).

Summary statistics, ANOVA, 90% confidence interval, ratio analysis, intra subject variability and power were calculated for Rivaroxaban. Geometric means and ratio of means were calculated for Rivaroxaban.

ANOVA was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Rivaroxaban.

All statistical analyses for Rivaroxaban were performed using PROC GLM of SAS® Release 9.4 (SAS Institute Inc., USA).

Results

Of the 48 subjects enrolled and randomised, 45 completed the clinical phase (completed both periods). Subject 20 was withdrawn due to vomiting in period I. Subject 42 and 48 were absent for period-II check-in. Samples of all 48 subjects were analysed for bioanalysis and included for PK analysis. 45 subjects were included in the statistical analysis.

Table 7. Pharmacokinetic parameters for rivaroxaban (non-transformed values, n=45)

Pharmacokinetic parameter		Test		Reference	
		arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	(ng/ml/h)	2776.76	650.857	2458.43	502.301
$AUC_{(0-\infty)}$	(ng/ml/h)	2800.66	649.157	2483.89	497.046
C_{max}	(ng/ml)	332.37	96.912	328.12	74.811
T_{max}*	(h)	4.50	2.00 - 14.00	3.50	0.50- 5.50
$t_{1/2}$	(h)	5.24	2.182	5.90	2.547
AUC_{0-t}	*area under the plasma concentration-time curve from time zero to t hours*				
$AUC_{0-\infty}$	*area under the plasma concentration-time curve from time zero to infinity*				
C_{max}	*maximum plasma concentration*				
T_{max}	*time for maximum concentration (* median, range)*				
$t_{1/2}$	*half-life*				

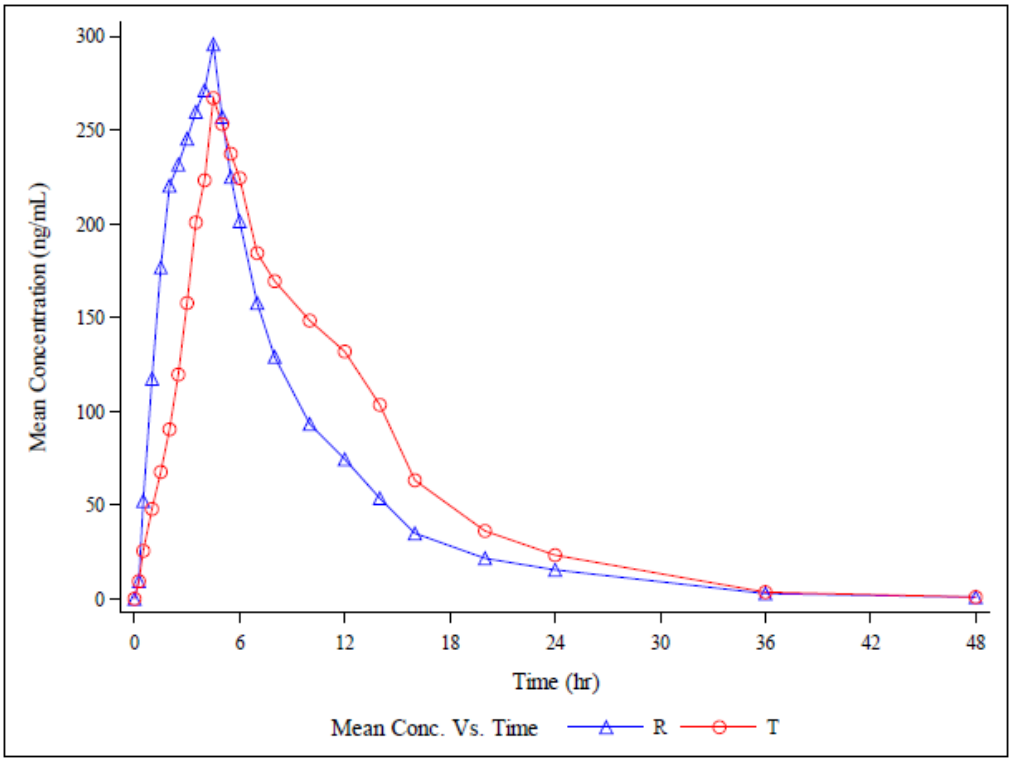
Table 8. Statistical analysis for rivaroxaban (ln-transformed values, n=45)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$	112.52	107.52 - 117.77	12.90
C_{max}	99.78	92.09 - 108.11	22.92
**Estimated from the Residual Mean Squares*			

The 90% confidence intervals for geometric least square means ratios of ln-transformed parameters C_{max} and AUC_{0-t} of Rivaroxaban was within the bioequivalence acceptance range of 80.00%-125.00%.

Based on the study results, Rivaroxaban Orodispersible Film 20 mg (Test) of Shilpa Medicare Limited, India is bioequivalent to Xarelto 20 mg (Rivaroxaban) film-coated tablets (Reference) of Bayer AG, 51368 Leverkusen, Germany in healthy, adult, human subjects under fed conditions.

Figure 3. Linear plot of mean plasma concentrations vs time profile of Rivaroxaban under fed conditions



For C_{max} and AUC_{0-t}:

Subject (Sequence) effect for ln-transformed data was found to be statistically significant at 5% level of significance for C_{max} and AUC_{0-t}. Treatment effects for ln-transformed data were found to be statistically significant at 5% level of significance for AUC_{0-t}.

The treatment effect in this study is due to random error alone. This may be explained by the fact that the point estimates of the ratios are direct results, whereas the Confidence Intervals are constructed around these point estimates using the estimated mean square error of the model. The resulted 90% CI for the pharmacokinetic parameters of AUC_{0-t} was within 80.00 - 125.00%, which are acceptable regulatory limits. Therefore, under these circumstances significant treatment effect could be ignored as it would not bias the bioequivalence, and it is unlikely to have clinical implication.

- ***Safety data***

A total of two adverse events were reported in two subjects during the entire duration of the study. One adverse event (vomiting) was reported in one subject (subject no. 20) during period-I and was observed in relation to the treatment (test product). One adverse event (increased SGPT) was reported in one subject (subject no. 30) during post study as lab abnormalities. The reported AEs were both mild in intensity.

No adverse events were reported during washout period and period-II.

No deaths or serious adverse events were reported during the study.

Overall, Rivaroxaban Orodispersible Film 20 mg was well tolerated as a single oral dose of 1 x 20 mg when administered under fed conditions.

Based on evaluation of adverse events, clinical laboratory evaluation and vital signs examination, it was concluded that both the Test product (T) and Reference product (R) were well tolerated and found to be safe.

2.4.2.2. Pharmacokinetic conclusion

Based on the presented bioequivalence studies Rivaroxaban Koanna 10 mg and 20 mg orodispersible films are considered bioequivalent with Xarelto 10 mg and 20 mg film-coated tablets.

The results of study 097/22 with the 10 mg formulation and study 013/24 with the 20 mg formulation can be extrapolated to the other strength 15 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

To support the application, the applicant submitted two bioequivalence studies (Study 097/22, 10 mg, and Study 013/24, 20 mg). A biowaiver is requested for the 15 mg strength based on the bioequivalence studies and *in vitro* dissolution data comparison. The BE studies for the 10 mg and 20 mg strengths in fasted and fed state, respectively, were performed following the EMA guidance *Rivaroxaban film-coated tablets 2.5, 10, 15 and 20 mg product-specific bioequivalence guidance* (EMA/CHMP/160650/2016, 1 April 2016). According to it, due to the different food effect at different strengths, studies with two strengths are required: one single dose study under fasting conditions with the 10 mg strength and one single dose study under fed conditions with the 20 mg strength.

Initially, authorisation of a 2.5mg strength was requested but was removed during the assessment.

The study populations, PK variables, statistical methods, analytical method as well as the acceptance ranges for bioequivalence used in the BE studies are in accordance with the *Bioequivalence guideline* (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The pre-set bioequivalence criteria were met for both studies.

The provided dissolution data are eligible to confirm the adequacy of waiving additional *in vivo* bioequivalence testing for the 15 mg strength.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies Rivaroxaban Koanaa 10 mg and 20 mg orodispersible films are considered bioequivalent with Xarelto 10 mg and 20 mg film-coated tablets.

The results of Study 013/24 with 20 mg formulation CAN be extrapolated to other strength 15 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP.

Table 11. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Haemorrhage
Important potential risks	Embryo-fetal toxicity
Missing information	Remedial pro-coagulant therapy for excessive haemorrhage Patients with atrial fibrillation (AF) and prosthetic heart valve

Proposed summary of safety concerns is in line with safety concerns defined for the reference product Xarelto (RMP version 14.3 dated 24-08-2023).

2.5.2. Pharmacovigilance plan

Table 9. Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Routine pharmacovigilance activities, including collection and reporting of adverse reactions and signal detection, are considered sufficient for the safety concerns of the product. No additional pharmacovigilance activities are proposed.

2.5.3. Risk minimisation measures

Table 10. Risk minimisation measures

Safety concern	Risk minimisation measures
Important Identified Risk: Haemorrhage	Routine risk communication: SmPC sections 4.3, 4.4, 4.5, 4.8 and 4.9 Indication specific differences are listed in the respective SmPCs Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 (Information on patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors is provided -monitoring for signs of bleeding complications. Information on groups of patients with an increased bleeding risk is provided. Information for surgery and interventions is provided - information on drug discontinuation. Information on patients with neuraxial (epidural/spinal) anaesthesia is provided - information on monitoring of epidural or spinal hematoma) SmPC section 4.5 (Information on pharmacokinetic interactions and pharmacodynamic interactions, food and dairy products) SmPC section 4.9 (Information on the management of overdose and bleeding complications is communicated) Other routine risk minimisation measures beyond PI: Package size limited, Prescription Only Medicine (POM)
Important Potential Risk: Embryo-fetal toxicity	Routine risk communication: SmPC sections 4.3, 4.6 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 (Information: Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy) Other routine risk minimisation measures beyond PI: none
Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk communication: SmPC section 4.9 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Risk minimisation measures
	Additional information for management of bleeding. Other routine risk minimisation measures beyond PI: limited package sizes, POM
Missing information: Patients with atrial fibrillation (AF) and prosthetic heart valve	Routine risk communication: SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other routine risk minimisation measures beyond PI: limited package sizes, POM

Additional risk minimisation measures

This medicine has for additional risk minimisation measures educational material for prescribers and patient alert card to increase awareness about the risk of bleeding during the treatment with rivaroxaban. Proposed additional risk minimisation measures are listed below.

Educational material for prescribers and patient alert cards

Objectives

The aim of the introduction of additional educational materials is to increase the awareness and reduction of the bleeding risk during treatment with rivaroxaban. The objectives of the label text are to prevent physicians from prescribing rivaroxaban to certain patient groups at high risk of bleeding, and to ensure that use of rivaroxaban in other patients with conditions or receiving treatments that can increase the risk of bleeding will be carefully monitored to minimise the risk of bleeding complications.

Rationale for the additional risk minimisation activity

The applicant proposes to provide the following additional risk minimisation material to increase the understanding of the safe and effective use of rivaroxaban, and to counsel patients who are either currently receiving rivaroxaban or in whom rivaroxaban treatment is planned. All healthcare professionals who are expected to use rivaroxaban are provided with the following items:

• Summary of Product Characteristics (SmPC)

• Prescriber guide

• Patient alert card

The Prescriber guide is complemented with the SmPC which helps to remind physicians about the need to monitor and perform testing on patients before and/or periodically after treatment for early detection of haemorrhage The patient alert card will be supplied as wallet-sized, to enable patients to readily carry them.

It contains the minimum necessary information to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency.

Target audience and planned distribution path

Prescribing physicians and patients receiving rivaroxaban are provided with the educational material as agreed in the individual country with the national competent authority (NCA) in each MS prior to rivaroxaban launch.

Also, the prescriber guide and patient alert card will be shared by Koanaa healthcare medical information team to HCPs/ Physician who can request the material to Koanaa healthcare email pharmacovigilance@koanaa.com or pharmacovigilance@shilpamedicare.com

Plans to evaluate the effectiveness of the interventions: Quantitative and qualitative medical assessment of haemorrhage cases received would be performed and observed periodically. Periodic analysis and haemorrhage risk details update in every periodic safety update report (PSUR).

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Capecitabine Koanaa 150 mg & 500 mg film-coated tablets and Xarelto 2.5 mg, 10 mg, 15 mg & 20 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of rivaroxaban film-coated tablets. The reference product Xarelto is indicated for:

- **2.5 mg**

In combination 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.
In combination 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.

- **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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis with two-period, two-treatment cross-over bioequivalence studies in healthy, adult subjects under fasting or fed conditions design. The studies design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Rivaroxaban Koanaa met the protocol-defined criteria for bioequivalence when

compared with the Xarelto. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range. Bioequivalence of the two formulations was demonstrated.

A benefit /risk ratio comparable to the reference product for Rivaroxaban Koanaa 10 mg, 15 mg and 20 mg orodispersible films can therefore be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rivaroxaban Koanaa is favourable in the following indication:

Rivaroxaban Koanaa 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. (See section 4.4 for haemodynamically unstable PE patients).

Rivaroxaban Koanaa 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. (See 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.

Rivaroxaban Koanaa 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. (See 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Rivaroxaban Koanaa. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Rivaroxaban Koanaa 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 [Text included in Annex III]

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 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 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 Koanaa 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 Annex III.