17 September 2020
EMA/550657/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rivaroxaban Accord

International non-proprietary name: rivaroxaban

Procedure No. EMEA/H/C/005279/0000

Note

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

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List of abbreviations

AE	Adverse event
ACS	Acute coronary syndrome
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the plasma concentration curve
BE	Bioequivalence
CAD	Coronary artery disease
C_{max}	Maximum concentration
CFU	Colony Forming Units
CV	Coefficient of variation
DVT	Deep vein thrombosis
EC	European Commission
ECG	Electrocardiogram
ERA	Environmental risk assessment
EU	European Union
FDA	Food and Drug Administration
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practise
GMP	Good Manufacturing Practise
HCV	Hepatitis C virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International non-proprietary name
IR	Infrared
KF	Karl Fisher
MO	Major Objection

NMR	Nuclear Magnetic Resonance
NMT	No more than
OGD	Office of generic drugs
PE	pulmonary embolism
Ph.Eur	European Pharmacopoeia
PK	Pharmacokinetics
PSD	Particle size distribution
PVC	Polyvinylchloride
QC	Quality control
SLS	Sodium laurilsulfate
SmPC	Summary of Product Characteristics
T_{max}	Time of the maximum measured plasma concentration
$T_{1/2}$	Elimination or terminal half-life
UV	Ultraviolet
VTE	Venous thromboembolism
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 29 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Rivaroxaban Accord, 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 31 January 2019.

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 Accord 2.5 mg

In combination with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

In combination with acetylsalicylic acid (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.

Rivaroxaban Accord 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.

Rivaroxaban Accord 15 and 20 mg

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.

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 studies 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
- 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 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: 0444-17, 0977-18 and 725-14

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Frantisek Drafi

The application was received by the EMA on	29 July 2019
The procedure started on	15 August 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 November 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	30 March 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 May 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 September 2020
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 Accord on	17 September 2020

2. Scientific discussion

2.1. Introduction

Rivaroxaban Accord film-coated tablets 2.5, 10, 15 and 20mg MAAs have been submitted according to the Article 10.1 of Directive 2001/83/EC, as amended (i.e. generic application) containing the same active substance in the same pharmaceutical form and strengths as the reference product. The reference product is Xarelto 2.5, 10, 15 and 20mg film-coated tablets, marketed by Bayer AG, that was first approved in the European Union on 30/09/2008 via centralised procedure (EU/1/08/472).

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. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

The indications applied for Rivaroxaban Accord are almost the same as those for the reference products:

Rivaroxaban Accord is indicated for**:**

2.5 mg:

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

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

10 mg:

For prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

15 mg and 20 mg:

For 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 ischemic attack and for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Accord Healthcare S.L.U. 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 planned to be established *in vivo* for strengths 2.5 mg, 10 mg and 20 mg providing results of 3 bioequivalence studies (Studies 0444-17, 0977-18 and 725-14) and *in vitro* for the 15 mg strength. A biowaiver for the 15 mg strength has been requested by the applicant based on the satisfactory bioequivalence study on 20 mg strength (Study No. 725-14) and *in vitro* dissolution data comparison.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 2.5 mg, 10 mg, 15 mg, 20 mg of rivaroxaban as active substance.

Other ingredients used for the tablet core are: lactose monohydrate, croscarmellose sodium, sodium laurilsulfate, hypromellose, cellulose (microcrystalline), silica (colloidal anhydrous), magnesium stearate. Other ingredients used for the film coating are: macrogol, hypromellose, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

The product is available in clear PVC/aluminium blisters or HDPE bottles fitted either with a white opaque child resistant polypropylene closure and induction sealing liner wad or with white opaque continuous thread polypropylene screw closure and induction sealing liner wad.

Active substance

General information

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

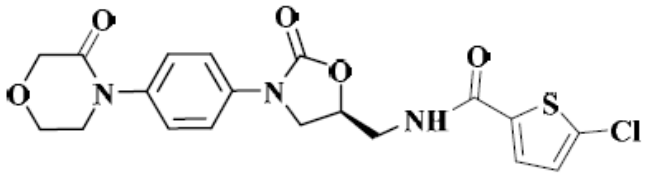

Figure 1: Rivaroxaban active substance structure

The chemical structure of rivaroxaban was elucidated by a combination of IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The solid-state properties of the active substance were measured by XRD.

The active substance is a non-hygroscopic, crystalline white to yellowish solid, soluble in dimethylsulphoxide and insoluble in water.

Rivaroxaban exhibits stereoisomerism due to the presence of one chiral centre. The *S*-isomer is the desired form. The required chiral centre is present in a starting material and is controlled routinely by chiral HPLC at release and on stability.

Polymorphism has been observed for rivaroxaban; rivaroxaban crystallizes in three polymorphs; thermodynamically stable form is used to manufacture the finished product. The same polymorphic form is manufactured by the ASMF holder and it is routinely controlled in the active substance specification by XRD.

Manufacture, characterisation and process controls

One active substance manufacturer, also responsible for testing, is proposed. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Rivaroxaban is synthesized in 6 main stages using 3 well-defined starting materials with acceptable specifications.

Adequate details of the micronisation step, performed by the manufacturer of the active substance, including in process steps and controls, were provided during the procedure. A specification limit for particle size in the applicant's part of the ASMF has also been introduced and stability data provided.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. In response to a MO raised during the procedure, the applicant has provided adequate data on the potential genotoxic impurities introduced intentionally in the synthesis (starting materials, reagents) or related to desired structures formed (intermediates containing structural alerts). Potential genotoxic structures that may arise in the synthesis of rivaroxaban have been identified and discussed in detail. The data provide, which take into consideration the control of starting materials, the potential level of genotoxic impurities present and their purge, confirm that no control is needed in the active substance specification.

No changes to the manufacturing process have been described in the manufacturing process development section.

The active substance is packaged in a transparent polyethylene bag, tied with strip seal, placed in a second transparent polyethylene bag, tied with a second strip seal, placed in triple laminated bag with heat seal and packed in HDPE drum. The polyethylene bag complies with the EC directive 2002/72/EC and meet the requirements of 3.2.2 and 3.1.3 of European Pharmacopoeia for various additives.

Specification

The active substance specification, includes tests for: description (in-house), solubility (Ph. Eur.), identification (IR, HPLC, XRD), water (Ph. Eur. -KF), sulphated ash (Ph. Eur.), related substances (HPLC), chiral related substance (HPLC), assay (HPLC), residual solvents (GC), particle size (Malvern analyzer) and microbiological examination (Ph. Eur.).

The specification includes all the test criteria of the draft rivaroxaban monograph, published in Pharmeuropa 30.4 (October 2018).

Description and solubility are included as descriptive tests. Identification is performed by three different methods: IR, HPLC and XRD, which ensures the consistency of polymorphic form.

The limits for water, sulfated ash and specific optical rotation are in line with the reported properties and Ph. Eur. method requirements. The limit for assay is also justified as in line with the reported properties and ICH Q6A. The limits for related substances are in line with the requirements of ICH Q3A and those of residual

solvents comply with ICH Q3C. No class 1 solvents are employed in the synthesis. The absence of a test for residual benzene in the active substance specification has been adequately justified.

The particle size limits were defined in order to ensure batch to batch consistency including consistency with the biobatches.

As rivaroxaban is manufactured as non-sterile active substance, microbiological quality limits for non-sterile substances are included in the specification.

The analytical methods used have been adequately described and non-compendial methods 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 data (4 production scale) of the active substance are provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale process validation batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification (IR and XRD), water (KF), related substances assay and particle size. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications for both the long term and accelerated stability data.

Photostability testing following the ICH guideline Q1B was performed on one batch confirming that the active substance is photostable. Results under stressed conditions (acid, alkali, oxidation, thermal, humidity, UV and fluorescent light degradation) were also provided to demonstrated that the assay and impurity tests are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is stable and justify the proposed retest period of 36 months when stored in the proposed container. Based on the data provided no specific storage conditions are required, however, the applicant choses to state: 'Preserve in air tight container and store at 25°C with excursions permitted to 15°C-30°C which is accepted as it is more restrictive than the stability conditions justified by the presented data.

Finished medicinal product

Description of the product and Pharmaceutical development

Rivaroxaban film-coated tablets are available in four strengths (2.5 mg, 10 mg, 15 mg and 20 mg). All the strengths have the same qualitative core composition. The tablets are distinguished by colour.

The aim of pharmaceutical development of Rivaroxaban 2.5/10/15/20 film-coated tablets was to develop a robust, stable and bioequivalent generic formulation of reference product Xarelto 2.5/10/15/20 mg film-coated tablets.

Formulation development was based on preliminary understanding of the molecule, literature data and reference product evaluation. As rivaroxaban active substance exhibits very low solubility in aqueous media through the whole pH range, sodium laurilsulfate is used as a solubilizer (SLS) in the composition of finished product. The excipients are qualitatively the same as those used in the reference product with the exception of colloidal anhydrous silica. As demonstrated by the dissolution and bioequivalence studies described below, the formulation difference is not considered significant. Compatibility between the active substance and the excipients has been confirmed through a binary compatibility study. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or NF (for the film-coating Opadry components). There are no novel excipients used in the finished product formulation. The use of colloidal anhydrous silica does not pose any concern from a safety perspective. The list of excipients is included in section 6.1 of the SmPC. No overages are used in formulation. The formulation used during clinical studies is the same as that intended for marketing.

The following process optimisation studies were executed: granulation time optimisation, lubrication time optimisation, hardness (resistance to crushing) optimisation and a speed challenge study.

The developed QC dissolution method initially proposed for all strengths in the application, is in line with Ph. Eur. requirements. The use of a surfactant is supported by literature and it was satisfactorily justified in line with the "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action." The composition of the routine QC dissolution medium for the 2.5 mg strength was amended by removing the surfactant, as requested during procedure, in view of the good solubility of the 2.5 mg strength in acetate buffer. The final proposed QC dissolution conditions for all the strengths are also the same as those described in the draft Ph. Eur. monograph for rivaroxaban tablets. The discriminatory power of the dissolution method has been demonstrated for the 10 mg strength and 20 mg strength. The QC dissolution tests proposed are considered satisfactory.

Bioequivalence studies were performed for the 2.5 mg, 10 mg and 20 mg showing bioequivalence between the clinical formulations and the proposed commercial formulation. Details on the bioequivalence studies conducted can be found in the clinical assessment.

Comparative dissolution profiles of the 2.5 mg, 10 mg and 20 mg Rivaroxaban test product film-coated tablets with the biobatches of reference product Xarelto in four dissolution media were provided for all strengths. For strengths of 10 mg and 20 mg dissolution profiles were found to be similar as the f_2 value is above 50.

Dissimilarity was observed for 2.5 mg tablets, which was, however, found bioequivalent *in vivo*.

For 15 mg Rivaroxaban film-coated tablets a biowaiver has been requested in line with the requirements of the Guideline on the Investigation of Bioequivalence (both the 15 mg and the 20 mg strengths are manufactured by the same manufacturer using the same manufacturing process, the qualitative composition is the same, the composition of the both strengths is quantitatively proportional, the *in vitro* dissolution profile is similar under identical conditions for the additional strengths). Dissolution profiles of test product biobatch of Rivaroxaban 20 mg film-coated tablets were compared to test product Rivaroxaban 15 mg film-coated tablets in four dissolution media and found to be similar as they showed f_2 value is above 50; the f_2 was not calculated for the acetate and SLS buffer as dissolution was more than 85% within the first 15 minutes. Since the rotation speed for the paddle apparatus used in the dissolution testing to support the

biowaiver was not compliant with the Guideline on the investigation of bioequivalence (EMEA/CPMP/EWP/QWP/ 1401/98 Rev. 1/Corr), additional dissolution testing data was provided during the procedure to address a major objection (MO). Similarity between the 15 mg strength and the proposed 20 mg biobatch was demonstrated using the paddle the apparatus at 50 rpm, and also testing at the 5 min time point, by means of the f_2, similarity was demonstrated despite the incomplete release of the active in the media. Similarity of the dissolution profiles at pH 1.2 (0.1N HCl) could not be concluded to be similar according to the requirements of the guideline as there was too much variability, more than 10% RSD, at the second sampling point. As a result, a further clinical MO was raised, which was satisfactorily resolved by reanalysing the *in vitro* data using bootstrapping as resampling method. The results showed that dissolution profiles of 20 mg biobatch and 15 mg test batch were found similar, as discussed in the clinical assessment. The data provided justify the biowaiver for the 15 mg strength.

The potential administration of the crushed finished product via gastric tubes as stated in section 6.6 of the SmPC was discussed in detail. *In vitro* studies on nasogastric and gastronomy tubes were carried out to demonstrate similarity between the test and the reference product in line with the FDA Draft Guidance on Rivaroxaban. The following aspects of the test product were compared against the reference product: particle size distribution, sedimentation depth, dose recovery, stability in water and apple sauce for the rivaroxaban suspension. Administration by enteral tube was found feasible and the results similar for the test and reference products, confirming acceptability of the statement in the SmPC.

The primary packaging is clear PVC/Aluminium blisters or HDPE bottles fitted either with a white opaque child resistant polypropylene closure and induction sealing liner wad or with white opaque continuous thread polypropylene screw closure and induction sealing liner wad. The materials comply with EC requirements. The choice of the container closure systems has been validated by stability data and they are considered adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: co-sifting of ingredients for dry mixing; wet granulation and drying; milling and blending with extra-granular excipients, compression, film-coating and packing. The process is considered to be a standard manufacturing process.

Process validation for Rivaroxaban 2.5/10/15/20mg film-coated tablets is performed on three commercial scale batches per strength. The hold times (for lubricated granules, core tablets and bulk film-coated tablets) was supported by data obtained from the validation batches, as discussed in the pharmaceutical development section. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), average weight of tablet (weight balance), identification (HPLC, UV), loss on drying (halogen lamp, in-house), dissolution (in-house), uniformity of dosage units (by content uniformity, in house assay with Ph. Eur.), related substances (HPLC), assay (HPLC) and microbial examination (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A, where relevant, and it is generally acceptable for this type of dosage form.

Based on a stability study, the polymorphic form does not need to be controlled in the release specification.

The limits for loss on drying, dissolution and impurities were tightened during the procedure. The limit for total impurities was tightened in line with the draft Ph. Eur. rivaroxaban finished product monograph.

The potential presence of elemental impurities in the finished product has been assessed using 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.

To address a MO, a risk assessment on the potential presence of nitrosamine impurities originating from the active substance, excipients, process equipment, cleaning agents and packaging materials was provided. No risk was identified by the finished product manufacturer. However, due to the use of nitrocellulose-based printing primer and over coat lacquer, supportive testing should be conducted to guarantee that no formation of nitrosamines can occur leading to contamination of the finished product. The applicant is recommended to provide batch analysis data for 6 pilot scale batches or 3 production scale batches of the finished product confirming the absence of nitrosamines prior to commercialisation (REC).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The suitability of the in-house test method for loss on drying has been adequately demonstrated. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for three full scale batches, which are also the stability and validation batches, are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three full scale batches per strength of finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) 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.

Samples were tested for the same parameters as in the release specifications with the exception of average weight of the tablet, identification and uniformity of dosage units, which are not part of the proposed stability specification. This is acceptable as these parameters are not affected during storage. The analytical procedures used are the same as those used at release and are stability indicating. No significant changes have been observed and all results comply with the proposed stability testing specification limits.

As rivaroxaban active substance shows polymorphism, samples of the 2.5 mg, 10 mg and 20 mg strength were analysed at initial and 6 months stability station in blister and bottle pack stored under accelerated (40°C / 75% RH) and long-term conditions (25°C / 60% RH). Observed X-ray diffractograms confirm the Rivaroxaban polymorphic form remains stable and unchanged.

In-use stability testing was carried out for strengths 2.5 mg and 10 mg tablets stored in the HDPE bottles. Test samples from the 30-count and 500-count HDPE bottles (with seal removed), stored at 25°C and 60 RH, were exposed at study conditions for 15 to 60 seconds daily for 30 days (30-count HDPE bottle) and 90 days (500-count HDPE bottle). The testing frequency and protocol are reflective of the expected clinical usage. All

results were in line with the specification. Hence, the inclusion of in-use shelf life in the SmPC is not deemed necessary as practically no changes were detected.

A forced degradation study was carried out by exposing samples of the 20 mg strength to acid, alkali, oxidative, thermal, UV and water hydrolysis conditions. Significant degradation was observed under alkali and acid conditions with the level of total impurities around 6–8%. No degradation was observed in other samples. The forced degradation study confirmed the stability-indicating nature of the methods for assay and related substances.

In addition, samples of the 2.5 mg, 10 mg and 20 mg strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability results indicate that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 2 years, without any specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products. No other excipients derived from animal or human origin have been used.

Discussion on chemical, and pharmaceutical aspects

The rivaroxaban active substance is documented in an ASMF which has been satisfactorily updated during the procedure with the relevant information on genotoxic impurities, to address a MO. Although there is no official Ph. Eur. monograph for rivaroxaban, the specification of the active substance includes adequate test methods generally in line with the draft monograph, published in Pharmeuropa 30.4. The finished product specification, including the QC dissolution test, are aligned with the draft monograph for rivaroxaban tablets published in Pharmeuropa 31.2 and are considered adequate. A satisfactory risk assessment on the potential presence of nitrosamine impurities was provided in response to a MO. Although no risk was identified, due to the use of nitrocellulose-based printing primer and over coat lacquer, the applicant is recommended to provide supportive data to confirm that no transformation of nitrosamines can occur into the finished product. The requested biowaiver for the 15 mg strength has been adequately substantiated during the procedure with data provided to address a MO.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

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. Data has been presented to give reassurance on viral/TSE safety.

Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to provide batch analysis data for 6 pilot scale batches or 3 production scale batches of the finished product confirming the absence of nitrosamines in the finished product prior to commercialisation (REC).

2.3. Non-clinical aspects

2.4. 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.

2.4.1. Ecotoxicity/environmental risk assessment

The applicant considered that the introduction of Rivaroxaban Accord manufactured by Accord Healthcare S.L.U. is unlikely to result in any significant increase in the combined sales volumes for all rivaroxaban containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar. However, from the data submitted and the trend for an overall increase in the sales of rivaroxaban containing products the CHMP recommended that the applicant should conduct an ERA in accordance with EMEA/CHMP/SWP/4447/00 corr.2.

2.4.2. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is acceptable since rivaroxaban is a well-known active substance and essential similarity is claimed to the reference product. There are no new nonclinical studies performed in support of the proposed application hence the presented Non-clinical Overview is considered sufficient for this type of MAA.

2.4.3. Conclusion on the non-clinical aspects

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

The CHMP recommended an ERA in accordance with EMEA/CHMP/SWP/4447/00 corr.2. should be conducted by the applicant.

2.5. Clinical aspects

2.5.1. Introduction

This is an application for tablets containing rivaroxaban. To support the marketing authorisation application the applicant conducted 2 bioequivalence study with cross-over design under fasting conditions and 1 bioequivalence study with cross-over design under fed conditions. These were the pivotal studies for the assessment.

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.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) have been taken into account.

GCP

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

A request for a waiver of a bioequivalence study for Rivaroxaban Accord 15 mg was submitted by the applicant according to the following general requirements [Ref: Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**]:

1. All the strengths i.e. 2.5, 10, 15 and 20 mg of the proposed pharmaceutical products are manufactured by the same manufacturer i.e. Intas Pharmaceutical Limited using the same manufacturing process,

2. The qualitative composition of Rivaroxaban Accord 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets are the same.

3. The composition of the 15 mg strength is quantitatively proportional to the 20 mg strength, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same

4.The dissolution profiles of 15 mg and 20 mg strengths are similar in four different pHs (**Table 2**).

Table 2. Comparative dissolution data for Rivaroxaban Accord film-coated tablets 20 mg versus Rivaroxaban film-coated tablets 15 mg

Dissolution Medium		Collection Time (minutes)							
		5	10	15	20	30	45	60	f_2
		% Drug Release (Mean)							
Rivaroxaban 20 mg film-coated tablets 12 of units Batch no. X07471	0.1 N HCL	18	25	28	30	35	39	42	NA
	Acetate buffer pH 4.5	24	35	40	42	44	45	46	
	Acetate buffer pH 4.5 + 0.2% SLS (QC media)	31	62	74	80	85	88	90	
	Phosphate buffer pH 6.8	21	27	31	33	37	38	40	
Rivaroxaban 15 mg film coated Tablet 12 of units Batch no. X07470	0.1 N HCL	17	26	30	34	40	47	51	63.7
	Acetate buffer pH 4.5	30	43	48	51	54	56	57	51.8
	Acetate buffer pH 4.5 + 0.2% SLS (QC media)	56	77	82	85	87	89	90	43.05
	Phosphate buffer pH 6.8	25	32	35	37	41	46	48	62.4

Calculated f2 was above 50 for pH 0.1 N HCl, 4.5 and 6.8 indicating comparative release pattern in those dissolution trials performed by the applicant. However, when assessing the dissolution profile in 0.1 N HCl medium at 50 rpm, it was observed that for the dissolution of 15 mg strength, %RSD for 2nd time point (10 min) is 10.69. According to the Guideline on the Investigation of Bioequivalence, f2 calculation is applicable when RSD or coefficient of variation of any product is less than 20% for the first time point and less than 10% from second to last time point. As the f2 calculation is not acceptable for this case, applicant was asked to use bootstrapping method to calculate the comparability of dissolution profiles between 20 mg strength and 15 mg strength at 0.1 N HCl medium at 50 rpm.

In acetate buffer pH 4.5 + 0.2% SLS, the f2 factor was below 50. As the similarity results without surfactant are more relevant for granting the biowaiver, f2 below 50 in the media with surfactant is acceptable as such.

As recommended by the CHMP, the applicant calculated comparability of dissolution profiles between 20 mg and 15 mg strength in 0.1 N HCl medium at 50 rpm using bootstrapping method. The summarized dissolution profile similarity results are as follows:

Statistics	Value
Observed f_2	64.371
Number of bootstrap	5000
Bootstrap mean	64.299
Bootstrap median	64.215
5% percentile	61.533
95% percentile	67.352
Skewness	0.264
Kurtosis	0.103
Is 5% percentile ¡Ý 50	Yes
Similarity of R and T	**Accept**

Based on above results, 20 mg bio batch (Batch no. X07471) and 15 mg test batch (Batch no. X07470) dissolution profiles in 0.1 N HCl can be considered as similar.

5. The pharmacokinetics of rivaroxaban is linear up to a 10 mg single dose, while in doses above 10 mg less than a proportional increase in exposure was noted after a single dose. The guideline specifies that for the drugs with non-linear pharmacokinetics characterized 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 (BE No. 0977-18) and 20 mg (BE No. 725-14) strengths, taking into the account the food recommendation and recommendation of the product specific rivaroxaban bioequivalence guideline.

Clinical studies

To support the application, the applicant has submitted 3 bioequivalence studies, Studies 0444-17, 0977-18 and 725-14.

Table 3. Tabular overview of clinical studies

Project No.	Study Title
0444-17	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 2.5 mg in normal, healthy, adult, human subjects under fasting conditions
0977-18	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 10 mg in normal, healthy, adult, human subjects under fasting condition
725-14	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 20 mg in normal, healthy, adult, human subjects under fed conditions

2.5.2. Pharmacokinetics

Study 0444-17: An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 2.5 mg in normal, healthy, adult, human subjects (male) under fasting conditions.

Methods

Study design

This was a comparative, randomised, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on normal, healthy, adult volunteers with a single dose

administration under fasting conditions. In each study period, subjects received a single oral dose of 2.5 mg of a rivaroxaban tablet (test or reference) after an overnight fast of at least 10 hours. The tablet was swallowed whole without chewing or crushing. A washout period of 5 days was maintained between the successive dosing days.

Plasma samples of subjects were assayed for parent compound rivaroxaban using an LC-MS/MS method.

This was an open label study, hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the Reference Product-R and Test Product-T to the individual subjects.

Clinical Study Dates

Study initiation date: 05 September 2018

Study completion date: 14 September 2018

Test and reference products

Rivaroxaban Accord 2.5 mg tablets manufactured by Intas Pharmaceuticals Limited, Matoda, India (batch No.X06941; exp. Date 03/2020) has been compared to Xarelto 2.5 mg tablets manufactured by Bayer AG (Batch No: BXHJSF1, exp. date 06/2019).

Population studied

As per protocol, 56, normal, healthy, adult, human subjects (male) who complied with all the inclusion criteria (non-smoking, between 18 and 45 years of age and having a Body Mass Index (BMI) between 18.5 and 30.0) and none of the exclusion criteria were the target population in the study No. 0444-17.

Three (03) subjects discontinued from the study on their own accord in Period-II. Information regarding missing samples has been submitted. Plasma samples of withdrawn Subjects were analysed as per protocol requirement.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for rivaroxaban, with concentrations ranging from 0.202 ng/mL to 125.198 ng/mL, to determine the concentrations of Rivaroxaban in the samples of all analysed subjects.

A detailed description of the operative procedures and the validation process were provided.

Pharmacokinetic Variables

Employing the estimated concentration vs. time profiles of rivaroxaban, the following pharmacokinetic parameters were calculated:

Primary PK Parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary PK Parameters: T_{max}, $AUC_{\_\%Extrap\_obs}$, λz and $T_{1/2}$

Statistical methods

Descriptive statistics was calculated and reported for the pharmacokinetic parameters of rivaroxaban.

ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are calculated and reported for Rivaroxaban. Using two-one sided tests for bioequivalence, 90% confidence intervals for the ratio of the geometric least squares means between drug formulations are calculated for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for rivaroxaban.

Criteria for conclusion of bioequivalence:

The 90% confidence intervals for the difference of means of ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for rivaroxaban had to fall within the acceptance range of 80.00 to 125.00% to conclude the test product was bioequivalent to the reference product under fasting conditions.

Results

The pharmacokinetic parameters of rivaroxaban for Test Product-T and Reference Product-R are summarized in **Table 4**.

Table 4. Pharmacokinetic parameters for rivaroxaban (non-transformed values) in Study 0444-17

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)[#]	2.000 (0.500 - 4.333)	1.750 (0.500 - 4.667)
C_{max} (ng/mL)	75.455 ± 16.3647	79.918 ± 15.2939
AUC_{0-t} (ng.h/mL)	537.369 ± 121.9739	529.444 ± 126.8736
$AUC_{0-\infty}$ (ng.h/mL)	541.872 ± 121.7316	533.602 ± 126.0689
λ_z (1/h)	0.144 ± 0.0241	0.147 ± 0.0238
$t_{½}$ (h)	4.973 ± 0.9145	4.862 ± 0.9160
AUC_%Extrap_obs (%)	0.879 ± 0.9008	0.858 ± 0.6829

[#]T_{max} are represented as median (min-max) value.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for rivaroxaban are summarized in **Table 5**.

Table 5: Pharmacokinetic parameters for rivaroxaban (ln-transformed values) in Study 0444-17

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	73.728	78.380	94.1	89.85 - 98.48	14.2	100.0
lnAUC_{0-t}	524.076	514.980	101.8	98.82 - 104.80	9.0	100.0
ln$AUC_{0-\infty}$	528.729	519.448	101.8	98.89 - 104.77	8.9	100.0

Safety data

Five (05) AEs were reported by four (04) subjects during the conduct of the study. Two (02) AEs were reported in Period-I, two (02) in Period-II and one (01) at post-study safety assessment. All the AEs were mild in nature. The subjects were followed up until the resolution of their AEs. The outcome of the one AE was unknown for one subject as he did not report for his post-study safety assessment and was considered as lost to follow-up. The causality assessment was judged as possible for three (03) AEs and as not related for two (02) AEs. There were no deaths, serious or significant AEs reported during the conduct of the study.

Study 0977-18: An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 10 mg in normal, healthy, adult, human subjects (male) under fasting conditions.

Methods

Study design

Study design was similar to that of Study 0444-17, but patients were split in two Groups (I and II) and the washout period between the dosing days of two consecutive periods was 13 days for Group I and 16 days for Group II.

Clinical Study Dates

Study initiation date: 01 April 2019 (Group I)

17 April 2019 (Group II)

Study completion date: 17 April 2019 (Group I)

06 May 2019 (Group II)

Test and reference products

Rivaroxaban Accord 2.5 mg tablets manufactured by Intas Pharmaceuticals Limited, Matoda, India (batch No.X06944; exp. Date 03/2020) has been compared to Xarelto 2.5 mg tablets manufactured by Bayer AG (Batch No: BXHTAJ2, exp. date 05/2020).

Population studied

As per protocol, 80, normal, healthy, adult, human subjects (male) who complied with all the inclusion criteria (non-smoking, between 18 and 45 years of age and having a Body Mass Index (BMI) between 18.5 and 30.0) and none of the exclusion criteria were the target population in the study No.0977-18.

Two (02) subjects did not complete the study. One discontinued from the study on his own accord in Period-II, and the other was withdrawn from the study on the grounds of emesis in Period-II. Plasma samples of both withdrawn Subject were also analysed as per protocol requirement.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for rivaroxaban, with concentrations ranging from 1.068 ng/mL to 601.353 ng/mL, to determine the concentrations of Rivaroxaban in the samples of all analysed subjects.

A detailed description of the operative procedures and the validation process were provided.

Pharmacokinetic Variables, Statistical methods

These were the same as in Study 0444-17.

Results

The pharmacokinetic parameters of rivaroxaban for Test Product-T and Reference Product-R are summarized in **Table 6**.

Table 6. Pharmacokinetic parameters for rivaroxaban (non-transformed values) in Study 0977-18

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	2.017 (1.000 - 4.684)	2.500 (0.500 - 4.350)
C_{max} (ng/mL)	200.617 ± 54.9034	228.059 ± 54.5476
AUC_{0-t} (ng.h/mL)	1464.858 ± 347.8037	1571.850 ± 398.5131
$AUC_{0-\infty}$ (ng.h/mL)	1504.532 ± 358.0940	1601.995 ± 400.6648
λ_z (1/h)	0.120 ± 0.0464	0.126 ± 0.0415
$t_{½}$ (h)	6.882 ± 3.4769	6.163 ± 2.2910
AUC_%Extrap_obs (%)	2.595 ± 2.6285	1.982 ± 1.8678

*T_{max} is represented as median (min-max) value.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for rivaroxaban are summarized in **Table 7**.

Table 7: Pharmacokinetic parameters for rivaroxaban (ln-transformed values) in Study 0977-18

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$\ln C_{max}$	194.212	222.187	87.4	82.37 - 92.76	22.4	100.0
$\ln AUC_{0-t}$	1421.592	1516.515	93.7	90.03 - 97.60	15.1	100.0
$\ln AUC_{0-\infty}$	1459.555	1547.228	94.3	90.63 - 98.19	15.0	100.0

Safety data

Two (02) AEs were reported by two (02) subjects during the conduct of the study. One (01) AE was reported in Period-II (Vomiting) and one (01) AE was reported during the post-study safety assessment (Alanine aminotransferase increased). Both the AEs were reported in the subjects after administration of Test Product-T. Both the AEs were mild in nature. One subject was followed up until the resolution of his AE. The outcome of the one AE was unknown for one subject as he did not report for his post-study safety assessment and was considered as lost to follow-up. The causality assessment was judged as possible for both the AEs. There were no deaths, serious or significant AEs reported during the conduct of the study.

Study 725-14: An open label, balanced, randomized, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study of two products of Rivaroxaban tablets 20 mg in normal, healthy, adult, human subjects (male) under fed conditions.

Methods

Study design

This was a comparative, randomised, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on normal, healthy, adult volunteers with a single dose administration under fed conditions. In each study period, subjects received a single oral dose of 20mg of a rivaroxaban tablet (test or reference) after high fat high calorie vegetarian breakfast. The tablet was swallowed whole without chewing or crushing. A washout period of 5 days was maintained between the successive dosing days.

Plasma samples of subjects were assayed for parent compound rivaroxaban using an LC-MS/MS method.

This was an open label study hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of the Reference Product-R and Test Product-T to the individual subjects.

Clinical Study Dates

Study initiation date: 11 October 2018

Study completion date: 20 October 2018

Test and reference products

Rivaroxaban Accord 20 mg tablets manufactured by Intas Pharmaceuticals Limited, Matoda, India (batch No.X07471; exp. Date 03/2020) has been compared to Xarelto 20 mg tablets manufactured by Bayer AG (Batch No: BXHLCG1, exp. date 03/2020).

Population studied

As per protocol, 52, normal, healthy, adult, human subjects (male) who complied with all the inclusion criteria (non-smoking, between 18 and 45 years of age and having a Body Mass Index (BMI) between 18.5 and 30.0) and none of the exclusion criteria were the target population in the study No. 0444-17.

Four (04) subjects discontinued from the study due to medical reasons in Period-II. One additional subject discontinued from the study form his own accord. Information regarding missing samples has been submitted. Plasma samples of withdrawn Subjects were analysed as per protocol requirement.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for rivaroxaban, with concentrations ranging from 1.062 ng/mL to 602.416 ng/mL, to determine the concentrations of Rivaroxaban in the samples of all analysed subjects.

A detailed description of the operative procedures and the validation process were provided.

Pharmacokinetic Variables, Statistical methods

These were the same as in Study 0444-17.

Results

The pharmacokinetic parameters of rivaroxaban for Test Product-T and Reference Product-R are summarized in **Table 8**.

Table 8. Pharmacokinetic parameters for rivaroxaban (non-transformed values) in Study 725-14

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)[#]	4.333 (1.250 - 6.000)	4.333 (2.000 - 6.000)
C_{max} (ng/mL)	460.045 ± 124.2012	448.296 ± 127.6932
AUC_{0-t} (ng.h/mL)	3495.286 ± 945.4535	3411.367 ± 953.2469
$AUC_{0-\infty}$ (ng.h/mL)	3532.524 ± 948.6876	3437.147 ± 959.5661
λ_z (1/h)	0.128 ± 0.0390	0.135 ± 0.0318
$t_{½}$ (h)	6.043 ± 2.3579	5.497 ± 1.5894
AUC_%Extrap_obs (%)	1.109 ± 1.5841	0.754 ± 0.6849

[#]T_{max} is represented as median (min-max) value.

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for rivaroxaban are summarized in **Table 9**.

Table 9: Pharmacokinetic parameters for rivaroxaban (ln-transformed values) in Study 725-14

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	445.998	434.223	102.7	98.31 - 107.31	12.8	100.0
$lnAUC_{0-t}$	3379.647	3307.606	102.2	99.15 - 105.30	8.8	100.0
$lnAUC_{0-\infty}$	3417.555	3332.706	102.5	99.52 - 105.66	8.7	100.0

Safety data

Four (04) adverse events (AEs) were reported by three (03) subjects during the conduct of the study. One (01) AE was reported in Period-I (Pyrexia) and three (03) AEs were reported in Period-II (Pyrexia, Diarrhoea and Activated partial thromboplastin time prolonged) of the study. All AEs were reported in the subjects after administration of Test Product-T. All AEs were mild in nature and the subjects were followed up until AE resolution. The causality assessment was judged as probable/likely for one (01) AEs and as unlikely for three (03) AEs. There were no deaths or serious AEs reported during the conduct of the study.

2.5.3. Pharmacodynamics

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

2.5.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5.5. Discussion on clinical aspects

In support of this application, review of the published literature and three bioequivalence studies were submitted claiming essential similarity to the reference medicinal product Xarelto.

Submitted bioequivalence studies were randomised, single dose, two treatment, two period, two-way crossover open label studies comparing two formulations of rivaroxaban in healthy adults. Studies with 2.5 mg strengths and 10 mg strengths were done in fasted state, study with 20 mg strength was done under fed conditions. The studies were acceptable and in line with the existing EMA guidelines. In all three studies, statistical analysis demonstrated bioequivalence between test product (Rivaroxaban Accord 2.5 mg, 10 mg and 20 mg) and reference product (Xarelto). Submitted studies were claimed to be carried out according to the GCP principles by applicant.

With regard to the used bioanalytical methods for the three studies, the provided information was adequately discussed and justified by the applicant.

A biowaiver was requested for the 15 mg strength. The applicant submitted dissolution profiles between 15 mg strength and 20 mg strength by using paddle apparatus at 50 RPM speed (as requested by the CHMP). In 0.1 N HCl medium at this paddle apparatus speed, the dissolution of 15 mg strength, %RSD for 2nd time point (10 min) was 10.69. Thus, the applicant was asked to use bootstrapping to calculate the comparability of dissolution profiles between 20 mg strength and 15 mg strength at 0.1 N HCl medium at 50 rpm. Based on the results presented by the applicant, the dissolution profiles of the two strengths in 0.1 N HCl medium can be considered as similar.

2.5.6. Conclusions on clinical aspects

Based on the presented bioequivalence studies Rivaroxaban Accord 2.5mg, 10 and 20mg film coated tablets are considered bioequivalent with Xarelto 2.5 mg, 10 mg and 20 mg film coated tablets.

The results of study 725-14 with 20 mg rivaroxaban tablets can be extrapolated to the 15 mg rivaroxaban tablets according to conditions in the Guidelines.

2.6. Risk management plan

Safety concerns

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Risk minimisation measures
Important Identified Risks	
Haemorrhage	Routine risk minimisation measures: Section 4.2, 4.3, 4.4, 4.6, 4.8, 4.9 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: • Educational material for prescribers • Patient alert cards
Important Potential Risks	
Embryo-fetal toxicity	Routine risk minimisation measures: Section 4.3, 4.6, and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Missing information	
Patients with severe renal impairment (CrCl < 30 mL/min)	Routine risk minimisation measures: Section 4.2, 4.4 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Patients receiving concomitant	Routine risk minimisation measures:

Safety concern	Risk minimisation measures
systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	Section 4.5 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimisation measures: Section 4.9 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Pregnant or breast-feeding women	Routine risk minimisation measures: Section 4.3, 4.6 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimisation measures: Section 4.4 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	Routine risk minimisation measures: Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None

Safety concern	Risk minimisation measures
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine risk minimisation measures: Section 4.2, 4.3 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None
Patients < 18 years	Routine risk minimisation measures: Section 4.2 and 5.2 of Rivaroxaban SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.7. Pharmacovigilance

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.

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.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has

been submitted by the applicant and has been found acceptable for the following reasons:

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 Xarelto 2.5/10/15/20 mg film-coated tablets and Solifenacin succinate 5/10 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 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 acetylsalicylic acid (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 and 20 mg

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.

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 a two-period, two-treatment cross-over bioequivalence study in healthy, adult subjects under fasting or fed conditions design. The study designs were 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 Accord met the protocol-defined criteria for bioequivalence when compared with Xarelto. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

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

Rivaroxaban Accord 2.5 mg

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

Co-administered with acetylsalicylic acid (ASA), 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 Accord 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.

Rivaroxaban Accord 15 and 20 mg

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.

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 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 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 Accord. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Rivaroxaban Accord 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 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 Accord 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.