16 September 2021
EMA/560715/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rivaroxaban Mylan

International non-proprietary name: rivaroxaban

Procedure No. EMEA/H/C/005600/0000

Note

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

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Administrative information

Name of the medicinal product:	Rivaroxaban Mylan
Applicant:	Mylan Ireland Limited Unit 35/36 Grange Parade Baldoyle Industrial Estate Dublin 13 IRELAND
Active substance:	Rivaroxaban
International Nonproprietary Name/Common Name:	rivaroxaban
Pharmaco-therapeutic group (ATC Code):	ANTITHROMBOTIC AGENTS, Direct factor Xa inhibitors (B01AF01)
Therapeutic indication(s):	Rivaroxaban Mylan, 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) (2.5 mg) Rivaroxaban Mylan, 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 (2.5 mg).

	Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (10 mg). 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) (10 mg, 15 mg, 20 mg and 15 mg + 20 mg initiation pack). 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 (15 and 20 mg). 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 (15 mg). 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 (20 mg).
Pharmaceutical form(s):	Film-coated tablets
Strength(s):	2.5 mg, 10 mg, 15 mg and 20 mg
Route(s) of administration:	Oral use
Packaging:	Blister (PVC/PVdC/alu), Bottle (HDPE)

Package size(s):	10 tablets, 10 x 1 tablets (unit dose), 100 x 1 tablets (unit dose), 14 tablets, 14 x 1 tablets (unit dose), 28 tablets, 28 x 1 tablets (unit dose), 30 tablets, 30 x 1 tablets (unit dose), 42 tablets, 42 x 1 tablets (unit dose), 50 x 1 tablets (unit dose), 56 tablets, 56 x 1 tablets (unit dose), 60 tablets, 60 x 1 tablets (unit dose), 90 x 1 tablets (unit dose), 98 x 1 tablets (unit dose), Initiation pack: 49 tablets (42 x 15 mg + 7 x 20 mg), 100 tablets, 196 tablets and 98 tablets

Table of contents

1. Background information on the procedure 10
1.1. Submission of the dossier 10
1.2. Legal basis, dossier content 11
1.3. Information on paediatric requirements 12
1.4. Information relating to orphan market exclusivity 12
1.4.1. Similarity 12
1.5. Scientific advice 12
1.6. Steps taken for the assessment of the product 12

2. Scientific discussion 13
2.1. Introduction 13
2.2. Quality aspects 15
2.2.1. Introduction 15
2.2.2. Active substance 16
2.2.3. Finished medicinal product 18
2.2.4. Discussion on chemical, and pharmaceutical aspects 22
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 22
2.2.6. Recommendation(s) for future quality development 22
2.3. Non-clinical aspects 23
2.3.1. Introduction 23
2.3.2. Ecotoxicity/environmental risk assessment 23
2.3.3. Discussion on non-clinical aspects 23
2.3.4. Conclusion on the non-clinical aspects 23
2.4. Clinical aspects 23
2.4.1. Introduction 23
2.4.2. Clinical pharmacology 26
2.4.3. Discussion on clinical aspects 33
2.4.4. Conclusions on clinical aspects 33
2.5. Risk Management Plan 33
2.5.1. Safety concerns 33
2.5.2. Pharmacovigilance plan 34
2.5.3. Risk minimisation measures 34
2.5.4. Conclusion 36
2.6. Pharmacovigilance 36
2.6.1. Pharmacovigilance system 36
2.6.2. Periodic Safety Update Reports submission requirements 36
2.7. Product information 36
2.7.1. User consultation 36

3. Benefit-risk balance 36

4. Recommendations..... 38

List of abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial Fibrillation
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
aPTT	Activated Partial Thromboplastin Time
AR	Assessment Report
AS	Active Substance
ASA	Acetylsalicylic Acid
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AT	Antithrombin
AUC	Area Under the time-concentration Curve
BE	Bioequivalence
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHMP	Committee for Medicinal Products for Human Use
CrCl	Creatinine Clearance
CL/F	Apparent total clearance
Cmax	Maximum plasma concentration
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance
CV	Coefficient of Variation
DOAC	Direct Oral Anticoagulant
DR	Delayed release
DVT	Deep Vein Thrombosis
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment

EU	European Union
FP	Finished medicinal Product
GCP	Good Clinical Practice
GC-MS	Gas Chromatography Mass Spectrometry
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HMLDPE	High Density & High Molecular High Density Polyethylene
HPLC	High Performance Liquid Chromatography
IBC	Intermediate bulk container
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	Indian Council of Medical Research
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In Process Control
IR	Infrared absorption
IS	Internal Standard
K_{el}	Elimination rate constant
KF	Karl Fischer titration
LCMS	Liquid Chromatography Mass Spectrometry
LDPE	Low Density Polyethylene
LLOQ	Lower Limit Of Quantitation
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
NA	Not Applicable
NMT	Not More Than
NMR	Nuclear Magnetic Resonance
PAD	Peripheral Artery Disease
PASS	Post-Authorisation Safety Study

PD	Pharmacodynamics
PDE	Permitted Daily Exposure
PE	Pulmonary Embolism
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PK	Pharmakocinetics
PL	Package Leaflet
POM	Prescription Only Medicine
PSD	Particle Size Distribution
PSMF	Pharmacovigilance System Master File
PT	Prothrombin Time
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
PXRD	Powder X-Ray Diffraction
QA	Quality Assurance
QTPP	Quality target product profile
RH	Relative Humidity
RMP	Risk Management Plan
rpm	Revolutions per minute
SLS	Sodium Lauryl Sulfate
SmPC	Summary of Product Characteristics
SPAF	Stroke Prevention in Atrial Fibrillation
$t_{1/2}$	Half-life
Tmax	Time for Maximum concentration
ULOQ	Upper Limit Of Quantitation
UV	Ultraviolet
VTE	Venous Thromboembolism
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 11 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Rivaroxaban Mylan, 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 26 March 2020.

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 Mylan 2.5 mg**

  Rivaroxaban Mylan, 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 Mylan, 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 Mylan 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 Mylan 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 Mylan 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.

- **Rivaroxaban Mylan 15 mg + 20 mg initiation pack**

  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.)

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 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 RIRO-TFZ-1001, Study RIRO-1-19112 and Study RIRO-1-19113

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: Konstantinos Markopoulos

The application was received by the EMA on	11 September 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to	28 January 2021

the applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 2021
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	1 July 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 July 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	16 August 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 September 2021
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 Mylan on	16 September 2021

2. Scientific discussion

2.1. Introduction

Rivaroxaban Mylan tablets 2.5, 10, 15 and 20 mg 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 20 mg 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 Mylan are the same as those for the reference products:

Rivaroxaban Mylan is indicated for:

- **Rivaroxaban Mylan 2.5 mg**

Rivaroxaban Mylan, 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 Mylan, 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 Mylan 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 Mylan 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 Mylan 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.

- **Rivaroxaban Mylan 15 mg + 20 mg initiation pack**

  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.)

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

- **2.5 mg**

  Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hypromellose, sodium laurilsulfate, ferric oxide yellow (E172), and magnesium stearate

  Film-coat: poly(vinyl alcohol), macrogol 3350, talc, titanium dioxide (E171), ferric oxide yellow (E172)

- **10 mg**

  Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hypromellose sodium laurilsulfate, and magnesium stearate

  Film-coat: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide (E171), and ferric oxide red (E172)

- **15 mg**

  Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hypromellose, sodium laurilsulfate, and magnesium stearate

  Film-coat: poly (vinyl alcohol), macrogol 3350, talc, titanium dioxide (E171) and ferric oxide red (E172)

- **20 mg**

  Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hypromellose, sodium laurilsulfate, and magnesium stearate

  Film-coat: poly (vinyl alcohol), macrogol 3350, talc, titanium dioxide (E171), and ferric oxide red (E172)

The product is available in PVC/PVdC/Aluminium foil blister packs or perforated unit dose blisters and white HDPE bottles with white opaque PP screw cap with aluminium induction sealing liner wad 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 or 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide corresponding to the molecular formula $C_{19}H_{18}ClN_3O_5S$. It has a molecular weight of 435.88 and the following structure:

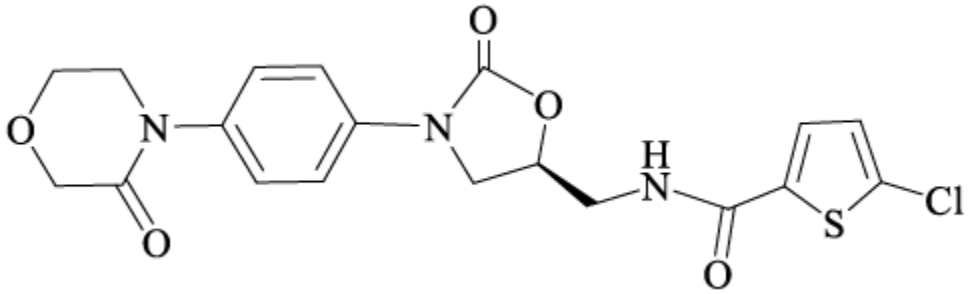

Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of elemental analysis, IR, UV, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and PXRD.

The active substance is a white or yellowish non-hygroscopic powder practically insoluble in water, freely soluble in dimethyl sulfoxide, practically insoluble in anhydrous ethanol and in heptane.

Rivaroxaban has one chiral centre. It exhibits two structural isomers R and S. The commercial active substance has S absolute configuration. R isomer is formed by regioselective synthetic reaction and it is controlled in the active substance specification.

Rivaroxaban exhibits polymorphism and different forms i.e., Modification-I, Modification-II, Modification-III, Hydrate and NMP solvate are reported in the literature. The drug substance manufacturer consistently produces single polymorphic form of Rivaroxaban.

Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturing sites.

Detailed information on the manufacturing of the active substance by both manufacturers has been provided in the restricted part of the ASMFs and it was considered satisfactory.

The manufacturing procedures are essentially the same for both manufacturers with the exception of some solvents and reagents.

Rivaroxaban is synthesized in 5 main stages.

Data on micronisation procedure (analytical method, batch analysis and validation of method) was provided. Active substance manufacturers apply no batch reprocessing. Moreover, no recycled solvents (entailing the formation of secondary amines in the frame of nitrosamine control) are used.

Adequate in-process controls and control of critical steps are applied during the manufacturing procedure. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Solvents and reagents are presented with adequate specifications. No recovery and reuse of solvents was applied.

The characterisation of the active substance from both manufacturers and its impurities is in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were extensively discussed with regard to their origin and characterised. Carry-over of the starting materials themselves to rivaroxaban has been adequately studied. The discussion and control of possible degradation impurities of rivaroxaban were provided and considered satisfactory. Data on the active substance genotoxic impurities was presented and considered satisfactory.

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

The active substance manufactured by the manufacturer-1 is packaged in LDPE bag twist and tied. Further it is inserted in HMLDPE bag and heat sealed. Both these bags are then put into the outer bag of triple laminated aluminium bag and heat sealed. These polybags are further packed in HDPE drums, closed with plastic lids having rubber gasket followed by locking ring, seal and labelled. All the materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

The active substance manufactured by the manufacturer-2 is packaged in transparent under nitrogen purging. The transparent bag is placed in a black LDPE bag. This pack is finally put in a HPDPE drum. All the materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification used by the manufacturer of the finished product shown in Table 1 includes tests for appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (KF), sulfated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), enantiomeric purity (HPLC), residual solvents (GC-MS), formic acid (HPLC), particle size (Malvern), melting point (Ph. Eur.), specific optical rotation (Ph. Eur.), microbial test (Ph. Eur.) and identification (PXRD).

The specifications are in accordance with the Ph. Eur. monograph on rivaroxaban, supplemented with more tests on PXRD, residual solvents, melting point, specific optical rotation and formic acid. During the procedure the tests for microbial quality and PSD were added and the limit for total impurities was tightened to NMT 0.30%, according to Ph. Eur. Monograph.

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 of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from several commercial scale batches of active substance manufactured by manufacturer-1 stored in the intended commercial package for up to 18 months under long term conditions (25±2°C/60±5% RH) and for up to 6 months under accelerated conditions (40±2°C/75±5% RH) according to the ICH guidelines were provided.

Stability data from several commercial scale batches of active substance manufactured by manufacturer-2stored in the intended commercial package for up to 24 months under long term conditions (25±2°C/60±5% RH) and for up to 6 months under accelerated conditions (40±2°C/75±5% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, loss on drying, water content, related substances, enantiomeric purity (specific optical rotation) and assay. The analytical methods used were the same as for release and were stability indicating. All results were found within the proposed limits and no significant changes were observed in the active substance manufactured by both manufacturers.

Stress studies (acid hydrolysis, base, hydrolysis, oxidation, and heat degradation, thermal (105°C -24 Hrs) and after 24 hrs exposure at 90 ±5% RH)) have been performed and changes in assay and related compounds have been found and evaluated. The methods for assay, enantiomeric purity and related compounds have been demonstrated to be stability indicating.

Photostability study of one batch of rivaroxaban according to ICH Q1B guideline was performed and showed that the active substance is photostable. Additionally, the active substance manufacturers have demonstrated that the IR, XRD and chiral purity of the active substance remain unchanged during the stability period.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months without special storage conditions for the active substance manufactured by manufacturer-1 in the proposed container and 36 months without special storage conditions for the active substance manufactured by manufacturer-2 in the proposed container.

The finished product manufacturer, irrespective of the actual retest period approved for each active substance manufacturer (24 or 36 months), applies a more restrictive retest period without special storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as film coated biconvex, bevelled edge tablet, debossed with RX on onside of the tablet and 1 (2.5 mg), 2 (10 mg), 3 (15 mg) and 4 (20 mg) on other side.

Each tablet shape is round (2.5 mg tablets (approximately 5.4 mm), 10 mg (approximately 5.4 mm), 15 mg (approximately 6.4 mm), 20 mg (approximately 7.0 mm)). Strengths are also differentiated by colour (2.5 mg: light yellow to yellow, 10 mg: pink to brick red, 15 mg: pink to brick red and 20 mg: light pink to pink). Since the 10 mg and 15 mg strengths are differentiated only by the debossing and size, whilst shape (round) and colour (pink to brick red) are the same, to further reduce medication errors, the CHMP recommends to investigate any additional differentiation (colour and/or shape) in the future.

The purpose of the pharmaceutical development studies outlined below was to develop an essentially similar generic version of the reference medicinal product Xarelto film coated tablets, suitable for production scale batches (large-scale manufacture), exhibit reproducible results and demonstrate acceptable stability performance in the proposed marketing pack(s).

Based on the active substance properties and characterisation of reference product and its label, a quality target product profile (QTPP) that includes dissolution, uniformity of dosage units, related substance and other aspects of product quality and equivalence were identifiedThe active substance was analysed for particle size distribution, bulk density, tapped density, compressibility index, Hausner ratio, and solubility. Regarding solubility, relevant data indicate that rivaroxaban is practically insoluble across different pH range; however solubility increases with the addition of a surfactant.

To evaluate compatibility of selected excipients with the active substance, binary mixtures of the active substance and excipients were prepared with different ratios and exposed for defined period at 40°C ±2°C / 75 ± 5% RH in glass vials closed with rubber stopper with aluminum cap seal. The samples were evaluated for physical characteristics, assay and related substance at initial and after exposure. The results of the excipients compatibility studies indicate that there was no significant change in the physical appearance of the binary mixtures.

All of the excipients used are conventional pharmaceutical ingredients that comply with the requirements of the Ph. Eur. except coating materials. The coating materials are proprietary materials purchased from a qualified commercial supplier, to an agreed specification. The individual compendial components used in the manufacturing of coating materials comply with the monograph in Ph. Eur. / NF. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Based on identified QTPP, the formulation development was initiated for the finished product. The product development involved identifying a feasible prototype formulation followed by optimisation studies for all the relevant formulation and process parameters.

The optimisation studies were carried out for prototype formulation composition and manufacturing process; they consist optimisation of: diluent concentration, binder concentration, wetting agent, lubricant concentration, disintegrating agent concentration, coating build up and active substance particle size.

The speed of the paddle apparatus, the buffer choice and surfactant concentration have been adequately justified for all strengths as they are needed to maintain sink conditions and the adequate buffer capacity. The discriminatory nature of dissolution method was evaluated with changes in both composition and process parameters. The discriminatory power of the dissolution method has been demonstrated.

Various comparisons of dissolution profiles have been elaborated: dissolution profiles of the generic medicinal product Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets (manufactured by Mylan) and the reference medicinal product Xarelto film-coated tablets were generated in different dissolution media. In all the cases the dissolution profiles can be considered as similar.

A bioequivalence study between Rivaroxaban 2.5 mg, 10 mg and 20 mg film-coated tablets (manufactured by Mylan and the reference medicinal product Xarelto 2.5 mg, 10 mg and 20 mg film-coated tablets (Manufactured by Bayer AG) has been performed. The composition and manufacturing process of the test product used in the bioequivalence study is identical to the one proposed for commercial supplies. Bioequivalence is confirmed.

A biowaiver for Rivaroxaban 15 mg film-coated tablets was requested. Since the 15 mg strength fulfils all the requirements to waive the bioequivalence studies for additional strengths as mentioned in CPMP guideline on the Investigation of Bio-equivalence CPMP/EWP/QWP/1401/98- Rev 01 – January 2010, the bio-equivalence study results of Rivaroxaban 20 mg film-coated tablets can be extended to Rivaroxaban 15 mg film-coated tablets. The active substance has poor flow properties and low solubility. To improve the flowability of and dissolution of the active substance, wet granulation by rapid mixing was selected for the manufacturing of the finished product. The additional steps of the manufacturing process consist of: milling and sifting of the granules followed by lubrication, compression, and film coating.

According to the SmPC, tablets may be crushed and administered in a small amount of water via a gastric tube or may be crushed and mixed with apple puree immediately prior to use and administered orally. Relevant studies in order to demonstrate similarity between the test and the reference product after administration via a gastric tube have been provided during the procedure and considered satisfactory.

Relevant compatibility and stability studies have been provided by the applicant and considered satisfactory.

The primary packaging is PVC/PVdC/Aluminum foil blister packs or perforated unit dose blisters and white HDPE bottles with white opaque PP screw cap with aluminum induction sealing liner wad. 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.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 11 main steps

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The typical production scale batch size(s) proposed for each strength have been validated according to the proposed process validation protocol. Alternate batch sizes between submission and proposed production-scale batch sizes, will be fully validated before marketing. The process validation scheme is well accepted.

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), dimensions, identification (HPLC, UV), dissolution (HPLC), uniformity of dosage units (by content uniformity), assay (HPLC), related substance (HPLC), water (KF), microbial test (Ph. Eur), and color identification (chemical methods).

The release specification for the strengths is the same as the one for the 2.5 mg tablet with the exception of the description, dimension, colour identification and content the nominal assay.

The proposed specification tests are in line with guideline and Ph. Eur. requirements and suitable for an immediate release tablet. The specification limits have been fully justified. During the procedure, the limit for the dissolution test has been tightened.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on several batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the 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). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary. 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 several commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from several commercial scale batches per strength of finished product with the active substance manufactured by manufacturer-1 and manufacturer-2 stored under long term conditions (25°C / 60% RH) and under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches with active substance from manufacturer-1, have completed the stability study up to 6 months at accelerated condition and 12 months at long term condition and batches, with active substance from manufacturer-2, have completed the stability study up to 6 months at accelerated condition and 9 months at long term. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing, i.e., PVC/PVdC blister pack and HDPE bottle pack.

Samples were tested for description, water, related substance, dissolution, assay, and microbiological testing. The analytical procedures used are stability indicating. No significant changes have been observed and all parameters were within the specifications.

In-use stability studies were performed in the HDPE bottle The results were found to comply with finished product shelf life specification at the tested phases for all the test parameters. Based on results, an in-use shelf life of 180 days is agreed for this product.

An 'open pot' stability study was performed to examine the effect on product when continuously exposed to the environment (by loading the sample into open containers i.e., petri dish and exposed over a period of time at 25 $\pm$ 2°C / 60 $\pm$ 5% RH). The results of open pot stability study were found to comply with the finished product shelf life specifications for the test parameters studied. Hence, the product is found to be stable up to a period of 90 days at the studied open pot stability conditions.

In addition, film-coated tablets strength packed in i.e. PVC/PVdC blister and HDPE bottle pack was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products The study results indicated that there were no out of specification results observed for all test parameters; thus, it can be concluded that the finished product is not photosensitive.

Forced degradation / stress studies were performed during validation of the assay and related substances test methods.

Based on available stability data, the proposed shelf-life of 2 years and without storage conditions when stored in either of the primary packaging proposed for marketing as stated in the SmPC (section 6.3) are acceptable. In use shelf-life for the bottle once open 180 days.

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 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.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to investigate any additional differentiation (colour and/or shape) in the tablets in the future to further reduce medication errors since the 10 mg and 15 mg strengths are differentiated only by the debossing and size, whilst shape (round) and colour (pink to brick red) are the same. This point is being put forward and agreed as a recommendation for future quality development.

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. Recommendation(s) 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:

- To investigate any additional differentiation (colour and/or shape) in the future to further reduce medication errors since the 10 mg and 15 mg strengths are differentiated only by the debossing and size, whilst shape (round) and colour (pink to brick red) are the same.

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

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Rivaroxaban Mylan manufactured by Mylan Ireland Limited is considered 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.

2.3.3. 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 non-clinical studies performed in support of the proposed application hence the presented Non-clinical Overview is considered sufficient for this type of MAA.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Rivaroxaban Mylan 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.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing rivaroxaban. To support the marketing authorisation application the applicant conducted 3 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** (20 January 2010) as well as the Guideline on Bioanalytical method validation EMEA/CHMP/EWP/192217/09, Rev.1 Corr. 2** (21 July 2011).

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 film-coated tablets, suggesting that the bioequivalence study results of 20 mg strength can be extended to 15 mg film-coated tablets, according to *CPMP guideline on the Investigation of Bio-equivalence - CPMP/EWP/QWP/1401/98 Rev.1/ Corr* **, since the following holds:

1/ Both strengths of Rivaroxaban i.e. 15 mg and 20 mg film coated tablets, are manufactured by the same manufacturer at the same manufacturing site using same manufacturing process.

2/ The qualitative composition of both strengths is the same.

3/ The composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is same for both strengths.

4/ The dissolution profiles of 15 mg and 20 mg strengths are similar in three different pHs.

5/ The absorption kinetics of Rivaroxaban is linear within the therapeutic dose range.

6/ As per posology and method of administration, both 15 mg and 20 mg strengths are recommended to be taken with food.

The rationale for a biowaiver for the 15 mg strength was accepted.

Tabular overview of clinical studies

To support the application, the applicant has submitted 3 bioequivalence studies:

Study Identifier	Objectives of the study	Study design and Type of Control	Test product, Dosage Regimen Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of patients	Duration of treatment	Study Status, Type of Report
RIRO-TFZ-1001	To investigate the bioequivalence of Mylan's rivaroxaban 2.5 mg film-coated tablets to Xarelto 2.5 mg film-coated tablets of Bayer AG following a single oral dose of test product or reference product under fasting conditions.	A single-dose, randomized, balanced, two-treatment, two-period, crossover oral bioequivalence study in healthy adult human subjects	**Test product:** Rivaroxaban film-coated tablets, 2.5 mg, 1 × 2.5 mg, oral **Reference product:** Xarelto 2.5 mg film-coated tablets, 1 × 2.5 mg, oral	**Planned:** 60 subjects **Enrolled:** Group-I: 30 subjects (subject numbers 01-30) + 2 additional subjects (standby-I & standby-II) Group-II: 30 subjects (subject numbers 31-	Healthy, adult, human subjects	Single dose	Completed, abbreviated

				60) + 2 additional subjects (standby-III & standby-IV) **Dosed:** Group-I Period-1: 30 subjects Period-2: 28 subjects Group-II Period-1: 30 subjects Period-2: 30 subjects **Withdrawn:** 2 subjects (subject numbers 01 & 02) **Completed:** 58 subjects **Bio-sample analysed:** 58 subjects **PK and statistical data analysed:** 58 subjects			
RIRO-1-19112	To investigate the bioequivalence of Mylan's rivaroxaban 10 mg film-coated tablets to Xarelto 10 mg film-coated tablets of Bayer AG following a single oral dose of test product or reference product under fasting conditions.	A single-dose, randomized, balanced, two-treatment, two-period, crossover oral bioequivalence study in healthy adult human subjects	**Test product:** Rivaroxaban film-coated tablets, 10 mg, 1 × 10 mg, oral **Reference product:** Xarelto 10 mg film-coated tablets, 1 × 10 mg, oral	**Planned:** 32 subjects + 2 additional subjects (standby-I & standby-II) **Enrolled:** 32 subjects + 2 additional subjects (standby-I & standby-II) **Dosed:** Period-1: 32 subjects Period-2: 29 subjects **Withdrawn:** 3 subjects (subject numbers 25, 28 & 32) **Completed:** 29 subjects **Bio-sample analysed:** 29 subjects **PK and statistical data analysed:** 29 subjects	Healthy, adult, human subjects	Single dose	Completed, abbreviated
RIRO-1-19113	To investigate the bioequivalence of Mylan's rivaroxaban 20 mg film-coated tablets to Xarelto 20 mg film-coated tablets of Bayer AG	A single-dose, randomized, balanced, two-treatment, two-period, crossover oral bioequivalence study in healthy adult human subjects	**Test product:** Rivaroxaban film-coated tablets, 20 mg, 1 × 20 mg, oral **Reference product:**	**Planned:** 36 subjects + 2 additional subjects (standby-I & standby-II) **Enrolled:**	Healthy, adult, human subjects	Single dose	Completed, abbreviated

	following a single oral dose of test product or reference product under fed conditions.		Xarelto 20 mg film-coated tablets, 1 × 20 mg, oral	36 subjects + 2 additional subjects (standby-I & standby-II) **Dosed:** Period-1: 36 subjects Period-2: 34 subjects **Withdrawn:** 2 subjects (subject numbers 32 & 33) **Completed:** 34 subjects **Bio-sample analysed:** 34 subjects **PK and statistical data analysed:** 34 subjects			

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study RIRO-TFZ-1001: Single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fasting conditions, investigating the bioequivalence of Mylan's rivaroxaban 2.5 mg film-coated tablets to Xarelto 2.5 mg film-coated tablets of Bayer AG.

Methods

- **Study design**

RIRO-TFZ-1001 study was a single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fasting conditions, investigating the bioequivalence of Mylan's rivaroxaban 2.5 mg film-coated tablets to Xarelto 2.5 mg film-coated tablets of Bayer AG.

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 3 days was maintained between the successive dosing days.

Access to the randomization code was restricted to the pharmacist or delegated staff during clinical conduct, and was provided by the QA department to the medical writers for report writing purposes.

- **Test and reference products**

Rivaroxaban Mylan 2.5 mg film-coated tablets manufactured by Mylan has been compared to Xarelto 2.5 mg fil-coated tablets manufactured by Bayer AG, Leverkusen, Germany.

- **Population(s) studied**

This study was designed based on the known pharmacokinetics of Rivoraxaban and generally accepted standards for the conduct of bioequivalence studies.

As per protocol, 60 subjects were enrolled in the study (30 + 2 additional subjects in group-I and 30 + 2 additional subjects in group-II) who complied with all the inclusion criteria and none of the exclusion criteria

Two subjects withdrew consent before the second period of the study for personal reasons, and therefore 58 subjects completed clinical portion of the study.

Four protocol deviations occurred. The reported deviations from protocol have no impact on the outcome of the BE study.

- **Analytical methods**

The plasma samples of subjects were analysed using a validated LC-MS/MS method for rivaroxaban, over a concentration range of 1.001 ng/mL (Lower limit of quantitation - LLOQ) to 100.099 ng/mL (Upper limit of quantitation - ULOQ), 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}, K_{el} and $T_{1/2}$

- **Statistical methods**

Descriptive statistics of all the pharmacokinetic parameters were computed and reported for Rivoraxaban.

The summary statistics (for relevant pharmacokinetic parameters) were computed and reported for both test and reference products of Rivaroxaban.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Rivaroxaban were subjected to Analysis of Variance (ANOVA).

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

Table 1. Pharmacokinetic parameters for Rivaroxaban (non-transformed values)

Pharmacokinetic parameter	Test (n=58)		Reference (n=58)	
	mean	SD	mean	SD
$AUC_{(0-t)}$ (ng×h/mL)	348.685	88.8231	339.696	92.2465
$AUC_{(0-\infty)}$ (ng×h/mL)	360.023	92.7015	350.300	95.9131

Pharmacokinetic parameter	Test (n=58)		Reference (n=58)	
	mean	SD	mean	SD
C_{max} (ng/ml)	56.468	12.7237	56.900	12.6815
T_{max}* (h)	1.500	0.500 - 4.500	1.500	0.500 - 4.500
K_{el} (1/h)	0.180	0.0391	0.186	0.0388
$t_{1/2}$ (h)	4.037	0.9132	3.905	0.8556
$(AUC_{0-t}/AUC_{0-\infty})*100$	96.888	1.3662	96.988	1.0188

Table 2. Statistical analysis for Rivaroxaban (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	102.95	98.92 - 107.14	12.9
C_{max}	99.02	95.28 - 102.90	12.4
* estimated from the Residual Mean Squares			

- **Safety data**

Two AEs were reported by two subjects over the course of the study.

The two reported adverse events (Alanine aminotransferase increased) were mild in severity and possibly related to the study drug. They occurred during post study safety evaluation and cannot be definitively attributed to either of the treatments since testing was performed only at screening and study exit.

Increased alanine aminotransferase is a known adverse event for rivaroxaban, as in paragraph 4.8 of the originator and proposed PI increase in transaminases is characterised as common.

Overall, Rivaroxaban Mylan Tablets 2.5 mg and Xarelto 2.5 mg rivaroxaban film-coated tablets were well tolerated by subjects under fasting conditions.

Study RIRO-1-19112: single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fasting conditions, investigating the bioequivalence of Mylan's rivaroxaban 10 mg film-coated tablets to Xarelto 10 mg film-coated tablets of Bayer AG.

Methods

- **Study design**

RIRO-1-1912 was a single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fasting conditions, investigating the bioequivalence of Mylan's rivaroxaban 10 mg film-coated tablets to Xarelto 10 mg film-coated tablets of Bayer AG.

All subjects checked into the clinical facility on the day prior to dosing. Check-in occurred at least 10.50 hours prior to dose administration in each study period. On dosing day, each subject received either a single, oral dose of 10 mg of either test product (Rivaroxaban Tablets 10 mg) or a single oral dose of 10 mg of the reference product (Xarelto 10 mg film-coated tablets). Dosing occurred following an overnight fast of at least 10.00 hours. Following a minimum 09 days washout period, all subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization (period-2). Access to the randomization code

was restricted to the pharmacist or delegated staff during clinical conduct, and was provided by the QA department to the medical writers for report writing purposes.

- **Test and reference products**

Rivaroxaban Mylan 10 mg film-coated tablets manufactured by Mylan has been compared to Xarelto 10 mg film-coated tablets manufactured by Bayer AG, Leverkusen, Germany.

- **Population(s) studied**

This study was designed based on the known pharmacokinetics of Rivoraxaban and generally accepted standards for the conduct of bioequivalence studies.

As per protocol, 32 subjects were enrolled in the study (15 + 1 additional subjects in group-I and 15 + 1 additional subjects in group-II) who complied with all the inclusion criteria and none of the exclusion criteria

Three subjects were discontinued from the study, as they did not come to check-in to the facility for the period-2 of the study, hence were withdrawn from the study. Therefore 29 subjects completed the study.

Four protocol deviations occurred. The reported deviations from protocol have no impact on the outcome of the BE study.

- **Analytical methods**

The plasma samples of subjects were analysed using LC/MS/MS method. Rivaroxaban in human plasma was determined using Liquid Chromatography Mass Spectrometry (LCMS) technique over a concentration range of 1.001 (LLOQ) to 400.395 ng/mL (ULOQ). The analytical method was developed and validated over a concentration range of 1.000 to 399.996 ng/mL (VR-232) at Bioanalytical laboratory of CRC, Mylan.

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}, K_{el} and $T_{1/2}$

- **Statistical methods**

Descriptive statistics of all the pharmacokinetic parameters were computed and reported for Rivoraxaban.

The summary statistics (for relevant pharmacokinetic parameters) were computed and reported for both test and reference products of Rivaroxaban.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Rivaroxaban were subjected to Analysis of Variance (ANOVA).

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

Table 3. Pharmacokinetic parameters for Rivaroxaban (non-transformed values)

Pharmacokinetic parameter	Test (n=29)		Reference (n=29)	
	Mean	SD	mean	SD
$AUC_{(0-t)}$ (ng×h/mL)	1090.557	296.3647	1060.885	217.9627
$AUC_{(0-\infty)}$ (ng×h/mL)	1128.955	300.6474	1099.340	217.9592
C_{max} (ng/ml)	137.730	43.7044	148.662	33.1895
T_{max}* (h)	2.00	0.500-5.000	2.00	0.500-4.500
K_{el} (1/h)	0.099	0.0353	0.104	0.0424
$t_{1/2}$ (h)	8.012	3.2916	8.023	3.7772
$(AUC_{0-t}/AUC_{0-\infty})*100$	96.545	2.6530	96.441	3.0486

Table 4. Statistical analysis for Rivaroxaban (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.02	91.93 - 108.82	18.92
C_{max}	89.92	80.44 - 100.51	25.14
* estimated from the Residual Mean Squares			

- **Safety data**

One AE was reported over the course of the study.

The reported adverse event (Alkaline phosphatase increased) was mild in severity and possibly related to the study drug. The AE occurred during post study safety evaluation and cannot be definitively attributed to either of the treatments since testing was performed only at screening and study exit.

Increased alkaline phosphatase is a known adverse event for rivaroxaban, as it is mentioned in paragraph 4.8 of the originator and proposed PI as uncommon.

Overall, Rivaroxaban Tablets 10 mg and Xarelto 10 mg rivaroxaban film-coated tablets were well tolerated by subjects under fasting conditions.

Study RIRO-1-19113: single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fed conditions, investigating the bioequivalence of Mylan's rivaroxaban 20 mg film-coated tablets to Xarelto 20 mg film-coated tablets of Bayer AG

Methods

- **Study design**

RIRO-1-19113 was a single-dose, randomized, balanced, two-treatment, two-period, crossover oral BE study in healthy adult human subjects under fed conditions, investigating the bioequivalence of Mylan's rivaroxaban 20 mg film-coated tablets to Xarelto 20 mg film-coated tablets of Bayer AG.

All subjects checked into the clinical facility on the day prior to dosing. Check-in occurred at least 11 hours prior to dose administration for each study period. Following a supervised overnight fast of at least 10.00 hours, subjects had high fat high calorie non-vegetarian breakfast approximately 800-1000 kilocalories [240 mL whole milk, 65 g chicken minced and sautéed in butter, bread toasted with butter 60 g, 115 g hash brown potato sautéed in butter, eggs fried in butter 85 g], subjects completed the breakfast within 30 minutes and after breakfast, each subject received either a single, oral dose of 20 mg of either test product (Rivaroxaban Tablets 20 mg) or a single oral dose of 20 mg of the reference product [Xarelto 20 mg rivaroxaban film-coated tablets]. Dosing occurred following a 07 days washout period, all subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomization (period-2).

Access to the randomization code was restricted to the pharmacist or delegated staff during clinical conduct, and was provided by the QA department to the medical writers for report writing purposes.

- **Test and reference products**

Rivaroxaban Mylan 20 mg film-coated tablets manufactured by Mylan has been compared to Xarelto 20 mg film-coated tablets manufactured by Bayer AG, Leverkusen, Germany.

- **Population(s) studied**

This study was designed based on the known pharmacokinetics of Rivoraxaban and generally accepted standards for the conduct of bioequivalence studies.

As per protocol, 36 subjects were enrolled in the study (17 + 1 additional subjects in group-I and 17 + 1 additional subjects in group-II) who complied with all the inclusion criteria and none of the exclusion criteria

Two subjects were discontinued from the study, as they did not come to check-in to the facility for the period-2 of the study, hence were withdrawn from the study. Therefore 34 subjects completed the study.

Four protocol deviations occurred. The reported deviations from protocol have no impact on the outcome of the BE study.

- **Analytical methods**

The plasma samples of subjects were analysed using LC/MS/MS method. Rivaroxaban in human plasma was determined using LCMS technique over a concentration range of 1.001 ng/mL (LLOQ) to 600.593 ng/mL (ULOQ). The analytical method was developed and validated over a concentration range of 1.001 to 600.593 ng/mL (VR-232) at Bioanalytical laboratory of CRC, Mylan.

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}, K_{el} and $T_{1/2}$

- **Statistical methods**

Descriptive statistics of all the pharmacokinetic parameters were computed and reported for Rivoraxaban.

The summary statistics (for relevant pharmacokinetic parameters) were computed and reported for both test and reference products of Rivaroxaban.

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Rivaroxaban were subjected to Analysis of Variance (ANOVA).

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

Table 5. Pharmacokinetic parameters for Rivaroxaban (non-transformed values)

Pharmacokinetic parameter	Test (n=34)		Reference (n=34)	
	mean	SD	mean	SD
$AUC_{(0-t)}$ (ng×h/mL)	3235.976	661.9871	3230.684	704.8838
$AUC_{(0-\infty)}$ (ng×h/mL)	3267.991	653.3322	3254.184	705.2859
C_{max} (ng/ml)	360.767	66.3004	368.944	92.2295
T_{max}* (h)	4.50	1.00-7.00	4.50	1.00-10.00
K_{el} (1/h)	0.128	0.0330	0.132	0.0263
$t_{1/2}$ (h)	5.889	2.1546	5.477	1.2493
$(AUC_{0-t}/AUC_{0-\infty})*100$	98.92	1.58	99.24	0.57

Table 6. Statistical analysis for Rivaroxaban (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.47	95.30-105.91	12.9
C_{max}	99.07	93.01-105.52	15.4
* estimated from the Residual Mean Squares			

- **Safety data**

One AE was reported over the course of the study.

The reported adverse event (Aspartate aminotransferase increased) was mild in severity and possibly related to the study drug. The AE occurred during post study safety evaluation and cannot be definitively attributed to either of the treatments since testing was performed only at screening and study exit.

Increased aspartate aminotransferase is a known adverse event for rivaroxaban, as it is mentioned in paragraph 4.8 of the originator and proposed PI as uncommon.

Overall, Rivaroxaban Tablets 20 mg and Xarelto 20 mg rivaroxaban film-coated tablets were well tolerated by subjects under fasting conditions.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. The pharmacodynamics properties of the molecule are well known from the reference compound.

2.4.3. Discussion on clinical aspects

The Applicant has submitted three BE studies i.e. study RIRO-TFZ-1001 with 2.5 mg film-coated tablets in fasted state, study RIRO-1-19112 with 10 mg film-coated tablets in fasted state and study RIRO-1-19113 with 20 mg film-coated tablets in fed state. The BE study on the 20 mg strength was used to support a biowaiver for the 15 mg strength. The BE studies for the 2.5 mg and 10 mg tablets in fasted state and the 20 mg tablets in fed state 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 "*since there is a different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths, fasting study should be conducted for the lower strengths, and fed study for the higher strengths*".

The study population, PK variables, statistical methods as well as the acceptance ranges for bioequivalence used in the three 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 all three studies.

The analytical method used for the rivaroxaban concentration in plasma determination for all BE studies seems to be adequately presented and to follow the requirements of the "Guideline on Bioanalytical method validation" (EMEA/CHMP/EWP/192217/09). The Applicant has performed the standard validations for the analytical method.

The in vivo BE study for the strengths of 15 mg can be waived, as all biowaiver of strength criteria are fulfilled.

2.4.4. Conclusions on clinical aspects

Based on the three BE studies, it can be concluded that the Rivaroxaban Mylan 2.5 mg, 10 mg and 20 mg film-coated tablets are bioequivalent to the Xarelto 2.5 m, 10 mg and 20 mg film-coated tablets.

Since all the criteria for the biowaiver of strength for the Rivaroxaban Mylan 15 mg film-coated tablets are fulfilled, it can be concluded that the Rivaroxaban Mylan 15 mg film-coated tablets are bioequivalent to the Xarelto 15 mg film-coated tablets.

No safety issues have been identified during the BE studies.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Haemorrhage
Important potential risks	Embryo-fetal toxicity

Summary of safety concerns	
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

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to further characterise the safety concerns of the product.

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Haemorrhage	Routine risk minimization measures: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Additional risk minimisation measures: Educational material for prescribers and Patient Alert Card
Embryo-fetal toxicity	Routine risk minimization measures: SmPC sections 4.3, 4.6 and 5.3 PL section 2 Additional risk minimisation measures: None
Patients with severe renal impairment (CrCl < 30 mL/min)	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 5.2 PL section 2

Safety concern	Risk minimisation measures
	Additional risk minimisation measures: None
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)	Routine risk minimization measures: SmPC sections 4.4 and 4.5 PL section 2 Additional risk minimisation measures: None
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimization measures: SmPC section 4.9 PL section 3 Additional risk minimisation measures: None
Pregnant or breast-feeding women	Routine risk minimization measures: SmPC section 4.3, 4.6 and 5.3 PL section 2 Additional risk minimisation measures: None
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimization measures: SmPC section 4.4 PL section 2 Additional risk minimisation measures: None
Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	Routine risk minimization measures: None Additional risk minimisation measures: None
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine risk minimization measures: SmPC sections 4.2, 4.3 and 5.2 PL section 2 Additional risk minimisation measures: None
Patients < 18 years	Routine risk minimization measures: SmPC section 4.2 PL section 2 Additional risk minimisation measures: None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 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

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:

A QRD form for assessment of user testing bridging proposals [EMA/355722/2014] has been submitted. The Applicant successfully justified the grounds for bridging design/layout/format and content with those of the Parent PLs (Duloxetine Mylan and Xarelto, respectively) that have been approved after user testing. This approach is acceptable and no further user testing is required.

3. Benefit-risk balance

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

- **Rivaroxaban Mylan 2.5 mg**

  Rivaroxaban Mylan, 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 Mylan, 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 Mylan 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 Mylan 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 Mylan 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.

- **Rivaroxaban Mylan 15 mg + 20 mg initiation pack**

  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.)

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 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 Mylan met the protocol-defined criteria for bioequivalence when compared with the Xarelto. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, AUC_{0-72h}, 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. Recommendations

Outcome

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

- **Rivaroxaban Mylan 2.5 mg**

  Rivaroxaban Mylan, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus 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 Mylan, 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 Mylan 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 Mylan 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 Mylan 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.

- **Rivaroxaban Mylan 15 mg + 20 mg initiation pack**

  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.)

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 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 rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III of the PI]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
  - The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III of the PI.