COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/4916/001-004/DC

Date: 3 June 2021

This module reflects the scientific discussion for the approval of Rivaroxaban Intas. The procedure was finalised at 5-2-2021 For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets from Intas Pharmaceuticals Limited.

The 2.5 mg tablets co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, are indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Furthermore, when co-administered with ASA, the 2.5 mg tablet are 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.

The 10 mg tablets are indicated for 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.

The 15 mg and 20 mg tablets are indicated for the 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. Additionally, the 15 mg and 20 mg tablets are indicated for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Finally, the 15 mg and 20 mg tablets are indicated for the treatment of 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xarelto 2.5mg, 10 mg, 15 mg and 20 mg film-coated tablets (NL RVG 101535) which has been centrally registered by Bayer Pharma AG since 2008 (original product) via procedure EMEA/H/C/000944 with MAH Bayer Pharma AG and has MA number EU/1/08/472.

The concerned member states (CMS) involved in this procedure were Poland, Germany, France and the Netherlands.

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

II. QUALITY ASPECTS

II.1 Introduction

Rivaroxaban Intas 2.5 mg are light yellow coloured, round, biconvex, film coated tablets debossed with “IL4” on one side.

Rivaroxaban Intas 10 mg are light pink to pink coloured, round, biconvex, film coated tablets debossed with “IL1” on one side.

Rivaroxaban Intas 15 mg are red coloured, round, biconvex, film coated tablets debossed with “IL” on one side and “2” on other side.

Rivaroxaban Intas 20 mg are dark red coloured, round, biconvex, film coated tablets debossed with “IL3” on one side.

Each film-coated tablet contains as active substance 2.5 mg, 10 mg, 15 mg or 20 mg of rivaroxaban.

Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg and 20 mg are packed in clear PVC-aluminium blisters in cartons and HDPE bottles.

Not all pack sizes may be marketed.

The excipients for Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg and 20 mg are:

Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Hypromellose 2910
Sodium laurilsulphate
Silica, colloidal anhydrous
Magnesium stearate

Film-coat
Macrogol 4000
Hypromellose 2910 6 cps
Titanium dioxide (E 171)
Iron oxide red (E 172) for **Rivaroxaban Intas 10 mg and 15 mg**
Iron oxide yellow (E 172) for **Rivaroxaban Intas 2.5 mg and 20 mg**

Rivaroxaban 2.5 mg and 10 mg film-coated tablets are look-alike formulations and Rivaroxaban 15 mg and 20 mg film-coated tablets are dose-proportional formulations.

II.2 Drug Substance

The active substance is rivaroxaban, an active substance not described in any pharmacopoeia. A draft monograph has been published in Ph.Eur. 30.8 (April 2018). The active substance is white to yellowish crystalline powder and is not soluble in water. The active substance exhibits polymorphism. Form I is used. The molecule is chiral, but the S-isomer is predominantly formed. The R-isomer is adequately controlled in the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The synthesis consist of 5 chemical steps and 1 purification step. These are considered acceptable. The synthesis is in general sufficiently described. The drug substance is sufficiently characterized with regard to the chemical structure and regarding polymorphic form.

Quality control of drug substance

The active substance specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months).The retest period of 36 months is acceptable for rivaroxaban form-I (micronized), when preserved in air tight container and stored at 25°C with excursions permitted to 15°C-30°C.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the product development was to formulate robust, stable and bioequivalent generic formulation of Rivaroxaban film-coated tablets 2.5 mg, 10

mg, 15 mg and 20 mg to that of reference product Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets marketed by Bayer Pharma AG, Germany.

During development a number of characteristics of the drug substance, such as description, bulk density, solubility (at different pH), compressibility, particle size analysis, hygroscopicity, polymorphism etc. have been investigated to confirm their suitability. Furthermore, a compatibility study of rivaroxaban as a drug substance with different excipients was carried out.

Also, a description of the formulation development is given. This initially includes the description of the selection of the excipients and manufacturing process for the manufacturing of the 10 mg tablets. This is followed by the development of the other tablet strengths.

The MAH has performed three bioequivalence studies. Rivaroxaban 2.5 mg film-coated tablets (fasting condition), Rivaroxaban 10 mg film-coated tablets (fasting condition), and Rivaroxaban 20 mg film-coated tablets (fed condition). For the 15 mg tablet a biowaiver of strength is proposed. To support the results obtained in the bioequivalence study the MAH has provided comparative dissolution profiles in the media as required by the Bioequivalence Guideline, and also the proposed QC medium. However, not all results obtained in the *in-vitro* dissolution studies reflect the results obtained in the bioequivalence study. As per the Guideline on the Investigation of Bioequivalence, the MAH has discussed this discrepancy, and provided possible reasons for the dissimilarity.

To support the biowaiver of strength for the 15 mg tablets, comparative dissolution studies were performed in accordance with the Bioequivalence Guideline against the 20 mg tablets. Based on all results provided, the biowaiver of strength can be accepted for the 15 mg tablets. The MAH has also described the development of the QC dissolution method. The same method is proposed for the 10 mg, 15 mg, and 20 mg tablet strengths. However, a surfactant-free dissolution medium for the 2.5 mg tablets is proposed.

According to the instructions in the SmPC, the tablets may be crushed and administered through an enteral tube. This claim is adequately supported.

Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured through a wet granulation method. The granulate is then mixed with lubricant and glidant. Followed by tablet compression, film-coating, and packing.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches per tablet strength.

Control of excipients

The excipients comply with Ph. Eur. requirements, where possible. These specifications are acceptable. Tests and limits for functionality related characteristics are adopted, as appropriate.

Quality control of drug product

The product specification includes tests for description, average weight of tablets, identification of rivaroxaban, loss on drying, dissolution, uniformity of dosage units, related substances, assay, and microbial examination. The release and shelf-life limits are identical, except for the limit for loss on drying. The proposed tests and limits are deemed acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches per tablet strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production scaled batches per tablet strength stored at 25°C/60% RH (twelve months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in clear PVC-Alu blister and HDPE bottle packs. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

After twelve months long term and six months accelerated conditions, no significant changes are observed in any of the parameters measured in any of the tablet strengths, in any of the proposed packaging.

No clear trends are observed with the loss on drying results.

The provided stability results shows that Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg and 20 mg tablets meet the dissolution limit set as per the recommendations in the Reflection paper on Dissolution Specification for generic oral immediate release products. Hence, the proposed shelf-life of 2 years is acceptable for the tablets stored in blister and bottles in accordance with ICH Q1E Evaluation of stability data. Based on the presented data, the proposed storage condition of 'This medicinal product does not require any special storage conditions', is deemed acceptable. Based on the presented data, there is no requirement to apply an in-use shelf-life for the HDPE bottles.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, except lactose monohydrate. Lactose monohydrate complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products. A theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rivaroxaban Intas has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Stability studies for the ongoing batches will be continued till the proposed shelf life as per the stability protocol presented in the dossier.
- Drug product manufacturer commits to place annually one batch per strength on long term stability study, if manufactured. Any results, which are out of specification, shall be reported to the authorities.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, no further studies are required and the MAH provides none. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban Intas is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clinical efficacy and safety of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, the MAH has not provided additional studies, besides bioequivalence studies, and further studies are not required. Overview based on literature review is, thus, appropriate. The submitted clinical overview on the clinical pharmacology, efficacy and safety is adequate.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies:

- Study I : single dose bioequivalence study with the 2.5 mg tablet under fasting conditions.
- Study II : single dose bioequivalence study with the 10 mg tablet under fasting conditions.
- Study III : single dose bioequivalence study with the 20 mg tablet under fed conditions.

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product rivaroxaban (Intas Pharmaceuticals Limited) is compared with the pharmacokinetic profile of the reference product Xarelto (Bayer Pharma AG) under fasting and fed conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product Xarelto. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The design of the studies are acceptable.

Biowaiver

The MAH proposed a biowaiver of strengths for the 15 mg strength, based on the Guideline on the investigation of bioequivalence. The applied for biowaiver of strengths is acceptable, as the manufacturing process and qualitative composition of the strength is identical. All comparative dissolution tests supporting a biowaiver for the 15 mg strength were performed in accordance with the Guideline on Investigation of Bioequivalence.

Bioequivalence studies

Study I : single dose bioequivalence study with the 2.5 mg tablet under fasting conditions.

Design
This was a randomised, two-treatment, two-period, single dose crossover bioequivalence study. Fifty-six healthy male subjects, aged 22 - 44 years, were dosed in this study. Each subject received a single dose (1 x 2.5 mg tablet) of both the test and the reference rivaroxaban formulations. The tablets were administered with 240 ml water after an overnight fast. For each subject there were 2 dosing periods, separated by a washout period of at least 5 days.

Blood samples were taken pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Rivaroxaban Intas 2,5 mg tablet under fasted conditions.

Treatment N=53	**AUC_{0-t}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	537 ± 122	75 ± 16	2.0 (0.5 - 4.33)	5.0 ± 0.9
Reference	529 ± 127	80 ± 15	1.75 (0.5 – 4.67)	4.9 ± 0.9
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	0.94 (0.90 – 0.98)	X	X
CV (%)	9.0	14.2	X	X

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Results
Out of a total of 56, 53 subjects were eligible for pharmacokinetic analysis. Two subjects withdrew on their own accord before/in period II and one subject did not report to the facility for check-in for period II.

Study II: single dose bioequivalence study with the 10 mg tablet under fasting conditions.

Design

This was a randomised, two-treatment, two-period, single dose crossover bioequivalence study. Seventy-nine healthy male subjects, aged 18 - 44 years, were dosed in this study. Each subject received a single dose (1 x 10 mg tablet) of both the test and the reference rivaroxaban formulations. The tablets were administered with 240 ml water after an overnight fast. For each subject there were 2 dosing periods, separated by a washout period of 13 days for group I and 16 days for group II.

Blood samples were taken pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

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

Treatment N=77	**AUC_{0-t}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1465 ± 348	201 ± 55	2.0 (1.0 – 4.68)	6.9 ± 3.5
Reference	1572 ± 399	228 ± 55	2.5 (0.5 – 4.35)	6.2 ± 2.3
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	0.94 (0.90 – 0.98)	X	X
CV (%)	9.0	14.2	X	X

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

Results

Out of a total of 79, 77 subjects were eligible for pharmacokinetic analysis. One subject did not report to the facility for period II. One subject was withdrawn in period II due to an AE (vomiting).

Study III: single dose bioequivalence study with the 20 mg tablet under fed conditions.
This study was performed as both the 15 mg and 20 mg tablets are to be taken with food. As these two strengths are considered dose proportional, only one (20 mg strength) was investigated in a bioequivalence study under fed conditions.

Design
This was a randomised, two-treatment, two-period, single dose crossover bioequivalence study. Fifty-two healthy male subjects, aged 20 - 43 years, were dosed in this study. Each subject received a single dose (1 x 20 mg tablet) of both the test and the reference rivaroxaban formulations. The tablets were administered with 240 ml water 30 min after intake of a high fat high caloric breakfast. (Toast/Chana Chat/Vegetable cutlets and milk) For each subject there were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were taken pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Rivaroxaban Intas 20 mg tablet under fed conditions.

Treatment N=48	**AUC_{0-t}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	3495 ± 945	460 ± 124	4.33 (1.25 – 6.0)	6.0 ± 2.4
Reference	3411 ± 953	448 ± 128	4.33 (2.0 – 6.0)	5.5 ± 1.6
***Ratio (90% CI)**	1.03 (1.00 – 1.06)	1.03 (0.98 – 1.07)	X	X
CV (%)	8.7	12.8	X	X

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

Results
Out of a total of 52, 48 subjects were eligible for pharmacokinetic analysis. Three subjects were withdrawn from the study on medical grounds in period II. One subject was withdrawn in period II due to protocol non-compliance.

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Rivaroxaban Intas is considered bioequivalent with Xarelto.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rivaroxaban Intas.

Safety specification

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xarelto. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to

the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Xarelto, PT/H/0472. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rivaroxaban Intas 2.5 mg, 10 mg, 15 mg, and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xarelto. Xarelto is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivaroxaban Intas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5-2-2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse