CBG MEB

Public Assessment Report

Scientific discussion

Rivaroxaban Denk 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets

(rivaroxaban)

NL/H/3972/001-004/DC

Date: 24 April 2018

This module reflects the scientific discussion for the approval of Rivaroxaban Denk 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. The procedure was finalised on 16 October 2017. 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
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 Denk 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets from DENK PHARMA GmbH & Co. KG.

The 2.5 mg strength, 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

The 10 mg strength is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

The 15 mg and 20 mg strengths 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.
Both strengths are also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xarelto 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets which have been registered in the EEA by Bayer Pharma AG through centralised procedure EU/1/08/472/001-021, 023-038 since 30 September 2008.

The concerned member states (CMS) involved in this procedure were Germany and Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Rivaroxaban Denk is a round biconvex film-coated tablet:

- The 2.5 mg strength is a yellow coloured film-coated tablet engraved with ‘RVX’ on one side.
- The 10 mg strength is a pink coloured film-coated tablet engraved with ‘10’ on one side.
- The 15 mg strength is a red coloured film-coated tablet engraved with ‘15’ on one side.
- The 20 mg strength is a brown-red coloured film-coated tablet engraved with ‘20’ on one side.

The product contains as active substance 2.5 mg 10 mg, 15 mg or 20 mg of rivaroxaban.

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

The excipients are:
Tablet core - hypromellose (E464), sodium laurilsulfate, cellulose microcrystalline (E460), lactose monohydrate , croscarmellose sodium, magnesium stearate
film-coating – macrogol 3350, hypromellose (E464), titanium dioxide (E 171), iron oxide yellow (E 172; only the 2.5 strength) and iron oxide red (E 172; only the 10 mg, 15 mg and 20 mg strengths)

The 2.5 mg and 10 mg strengths, as well as the 15 mg and 20 mg strengths, are dose weight proportional.

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off white powder. Rivaroxaban is insoluble in

acetone, practically insoluble in methanol, very slightly soluble in tetrahydrofuran, slightly soluble in acetonitrile and glacial acetic acid and soluble in dimethylformamide and dimethyl sulfoxide. The active substance exhibits polymorphism, form-I is used.

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 starting materials and their specifications from both manufacturers are acceptable. The drug substance is sufficiently characterised with regard to the chemical structure. The intended polymorphic form (Form-I) is consistently manufactured.

Quality control of drug substance
manufacturer one - The active substance specification is considered adequate to control the quality. Particle size distribution has been included with the limits as employed by the drug product manufacturer. Batch analytical data demonstrating compliance with the currently proposed active substance specification have been provided.
manufacturer two - In general the drug substance specifications are considered acceptable. The four potential related substances are the four specified impurities in the drug substance specification, their specification limits are acceptable. All in-house methods for drug substance control by the manufacturer are adequately described and validated in the dossier.
drug product manufacturer - The proposed drug substance specification as applied by the drug product manufacturer is considered acceptable. All methods have been adequately validated. The batch analysis results (1 batch manufacturer one, two batches manufacturer two) do meet the set requirements including those on particle size.

Stability of drug substance
manufacturer one - The proposed re-test period of 60 months with no special storage condition is acceptable. Rivaroxaban is generally very stable at accelerated and long-term conditions and no specific degradation trends are being observed (including polymorphic stability). Analytical results were obtained with stability indicating methods.
manufacturer two - All long-term (36 months) and accelerated results (6 months) are meeting the set requirements. At the indicated time-points and during these stability periods the polymorphic form does not change: Form I was confirmed during all tests. Based on all stability data the claimed re-test period of 36 months can be accepted if stored in the proposed packaging without specific storage temperature condition.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were formulation trials, manufacturing process optimisation trials and comparative dissolution studies with the innovator product.
Two bioequivalence studies have been performed with the 10 mg and 20 mg strength. For the 2.5 mg and 15 mg a biowaiver has been requested. The test products (10 mg and 20 mg) used in the bioequivalence studies are acceptable in view of composition, manufacture and batch size. The 20 mg strength used in the bioequivalence study and the 15 mg strength have similar dissolution profiles under identical conditions.

Manufacturing process
The drug product is prepared by micronization and roller compaction, followed by compression and film-coating. The process is a standard manufacturing process. The manufacturing process has been

validated according to relevant European guidelines. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients, except the film-coat mixtures, are tested according to their Ph.Eur. monographs. Specifications for the film-coating mixtures are provided. These specifications are acceptable. The three film-coat mixtures comply with in-house specifications. Their components either comply with Ph. Eur. standards or with Commission Regulation (EU) No. 231/2012.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, water content, related substances, dissolution, assay, uniformity of dosage units by content uniformity, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies are provided for three batches per strength covering 12 months storage at 25°C/60% RH and six months at 40°C/75% RH. No significant changes have been observed. On basis of the data submitted, a shelf life was granted of 24 months. A specific storage condition is not required. The photostability study demonstrated that the tablets are not sensitive for light. Based on the results of the in-use stability study, no claim in the SmPC on in-use is warranted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal or human origin included in the drug product. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban Denk is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xarelto which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rivaroxaban is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

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

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Rivaroxaban Denk 10 mg and 20 mg film-coated tablets (DENK PHARMA GmbH & Co. KG., Germany) is compared with the pharmacokinetic profile of the reference product Xarelto 10 mg and 20 mg film-coated tablets (Bayer Pharma AG, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver is applied for the strengths of 2.5 and 15 mg tablets, based on the study with 10 and 20 mg tablets, respectively. The biowaiver request has been motivated by the MAH with the following arguments:

- Manufacturing process and manufacturer are the same
- Linear pharmacokinetics (fasted: up to about 15 mg, fed: up to 20 mg)
- Qualitative composition of the different strengths is the same
- Ratio between amounts of active substance and excipients is the same for both strengths
- The strength used in the bioequivalence study and the additional strength have similar dissolution profiles under identical conditions.

The biowaiver for the 2.5 mg and 15 mg strengths can be approved.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 10 mg strength under fasted conditions
Design
An open-label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 33 ± 7 years. Each subject received a single dose (10 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the wash-out period was long enough, sampling period long enough, and the sampling scheme adequate to estimate pharmacokinetic parameters.

Results
One subject withdrew consent and one subject did not report to the facility during period II admission. Therefore, 34 subjects completed at least two periods and were eligible for pharmacokinetic analysis.

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

Treatment N=34	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	1556.0 ± 387	1586.9 ± 376.8	199.9 ± 65.1	2.3 (0.5-4.7)
Reference	1567.0 ± 304.0	1592.9 ± 300.8	196.7 ± 51.4	2.2 (0.5-5.0)
***Ratio (90% CI)**	0.98 (0.93-1.04)	0.99 (0.93-1.04)	1.0 (0.91-1.09)	-
CV (%)	13.0%	12.6%	22%	-

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

**ln-transformed values*

Bioequivalence study II – 20 mg strength under fed conditions

Design

An open-label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 42 healthy male subjects, aged 28 ± 6 years. Each subject received a single dose (10 mg) of one of the two rivaroxaban formulations. The tablet was orally administered with 240 ml water after exactly 30 minutes after start of consuming a high fat high calorie breakfast on an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 8 days

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the wash-out period was long enough, sampling period long enough, and the sampling scheme adequate to estimate pharmacokinetic parameters.

Results

All 42 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=34	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	2424.3 ± 680	2446.7 ± 675.9	314.6 ± 78.5	4.3 (1.0-5.5)
Reference	2594.8 ± 639.0	2629.7 ± 645.3	349.7 ± 81.8	4.0 (1.0-4.7)
***Ratio (90% CI)**	0.92 (0.87-0.97)	0.92 (0.87 – 0.97)	0.90 (0.84 – 0.95)	--
CV (%)	13.4	12.6	15	--

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

**ln-transformed values*

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

Summary table of safety concerns as approved in RMP:

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal toxicity
Missing information	• Safety in patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery • Safety in patients with severe renal impairment (creatinine clearance <30 ml/min) • Remedial pro-coagulant therapy for excessive haemorrhage • Safety in patients receiving systemic treatment with Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors other than azole-anti-mycotics (e.g. ketoconazole) and Human Immunodeficiency Virus (HIV) protease inhibitors (e.g. ritonavir) • Safety in pregnant or breast feeding women • Safety in patients with AF (atrial fibrillation) secondary to significant valvular heart disease and a prosthetic heart valve • Safety regarding long term therapy with rivaroxaban for treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke prevention in patients with non-valvular atrial fibrillation (SPAF) and acute coronary syndrome (ACS) in real-life setting • Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Safety in patients <18 years of age

It is considered that additional risk minimisation measures are necessary for the safe and effective use of the product. The educational material contains the following key elements:

- Physician educational material including the following key elements:
  - The SmPC
  - Prescriber guide
    - 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 Xarelto if they need to have any surgery or invasive procedure.

▪ The proposed prescriber guide is also in line with the educational materials of the reference product.
▪ 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.

o Patient alert cards
▪ The MAH has provided the detailed contents of the patient alert card with the product information. The contents of the proposed alert card are in line with the contents of the alert card of the reference product and are therefore acceptable.
▪ The common Patient Alert Cards has been approved during the procedure as the content is mentioned in annex III of Xarelto.

- Patient information pack

The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xarelto. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The applicant submitted a full user testing report for Rivaroxaban Denk 15 mg/20 mg. The applicant submitted two separate bridging reports for Rivaroxaban Denk 2,5 mg and Rivaroxaban Denk 10 mg. The full user testing report and the bridging reports are acceptable.

User test
The questions addresses the key safety issues and concerns the presentation of information.
The results of this test indicate that the package leaflet is well structured and organised, generally easy enough to understand and written in a comprehensible manner. The test shows that the leaflet is readable and patients/users are able to act upon the information that it contains. This report also meets the legal requirements for Art. 59(3) of Directive 2001/83/EC (as amended).
The report conforms to the study design, principles and success criteria featured in the European Commission's document “Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use” (2009). Based on the above the package leaflet can be qualified as acceptable.

Bridging reports
The applicant submitted two separate bridging reports for Rivaroxaban Denk 2,5 mg and Rivaroxaban Denk 10 mg, bridging the package leaflet of these two strengths with the user-tested package leaflet of Rivaroxaban Denk 15 mg/20 mg. The dimensions of the mock-ups, the design, layout and style of writing of the PILs are identical. Furthermore, the leaflets are equally complex in terms of information for safe use. The differences between the parent package leaflet and the two daughter package leaflets have minor impact on the readability of the two daughter package leaflets.
For Rivaroxaban Denk 2,5 mg an additional focus test was performed. The results of this focus test are satisfactory.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivaroxaban Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 October 2017.

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