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Public Assessment Report

Scientific discussion

CZ/H/0836/001-004/DC
Rivaroxaban Zentiva

CZ/H/0837/001-004/DC
Xanirva

2.5 mg hard capsules
10 mg hard capsules
15 mg hard capsules
20 mg hard capsules

rivaroxaban

Date: 22.11.2021

This module reflects the scientific discussion for the approval of Rivaroxaban Zentiva and Xanirva. The procedures were finalised on 22.3.2020.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rivaroxaban Zentiva and Xanirva, from Zentiva, k.s.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.
The concerned member states involved in the procedure CZ/H/836/001-004/DC were France, Germany, Italy and Portugal and in the procedure CZ/H/837/001-004/DC the CMS were Bulgaria, Estonia, Latvia, Poland, Romania, Slovakia and United Kingdom. The Marketing authorisation Application was withdrawn in Lithuania by the Applicant before the Day 210.

There were also other procedures CZ/H/834/001-004/DC (CMS: FR, DE, IT, PT) and CZ/H/835/001-004/DC (CMS: BG, EE, LV, LT, PL, RO, SK, UK) by Zentiva k.s. containing rivaroxaban in a pharmaceutical form of film-coated tablets which were already approved on November 18th 2019.

The originator and reference medicinal product is Xarelto 2.5 mg, 10 mg, 15 mg, 20 mg, film-coated tablets from Bayer Pharma AG, Germany, authorised since 2008-09-30 via the centralised procedure (EU/1/08/472/025-035,041,046-047; EU/1/08/472/001-010,022,042-045; EU/1/08/472/011-016,023,036,038,048 and EU/1/08/472/017-021,024,037,039,049 respectively).

The product is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of atherothrombotic events, recurrent DVT and PE, venous thromboembolism. Specifically:

- Rivaroxaban 2.5 mg, 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.

- Also, Rivaroxaban 2.5 mg is co-administered with acetylsalicylic acid (ASA) and it 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 10 mg is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

- Rivaroxaban 15 and 20 mg is indicated for a 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. It is also indicated for the treatment of deep vein thrombosis and pulmonary embolism, and prevention of recurrent deep vein thrombosis and pulmonary embolism in adults.

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

The active substance rivaroxaban is well-known and frequently used active substance.

Rivaroxaban is a direct factor Xa inhibitor with a high selectivity. Moreover, rivaroxaban has no direct effect on platelet aggregation. Rivaroxaban is a drug with a low solubility.

Three studies were performed to prove the bioequivalence: 10 mg of rivaroxaban under fasting conditions, 20 mg of rivaroxaban under fed conditions and sprinkled capsules of 20 mg rivaroxaban under fed conditions. A biowaiver for 2.5 mg (to 10 mg strength) and 15 mg (to 20 mg strength) was applied.

The RMS was assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for this product.

No scientific advice was given to the Applicant for this medicinal product.

II. QUALITY ASPECTS

II.1 Introduction

The drug products Rivaroxaban Zentiva and Xanirva contain rivaroxaban as the active substance. They are presented as an immediate-release hard capsules containing 2.5 mg (10 mg, 15 mg and 20 mg) of rivaroxaban for oral use.
Other ingredients in the fill of capsule include lactose monohydrate, croscarmellose sodium, hypromellose, cellulose microcrystalline, magnesium stearate and sodium laurilsulfate. The capsule hard contains gelatine, titanium dioxide and colorants. Capsules are marked with black printing ink.
The capsules are packed in transparent PVC//Al blisters and Al/Al blisters that are conventional for the solid dosage form.

II.2 Drug Substance

The active substance is rivaroxaban. It is not described in the European Pharmacopoeia.
Rivaroxaban is sourced from two manufacturers. ASMF for drug substance was applied by both manufacturers of API.
The chemical name of the rivaroxaban is 5- chloro- *N*- ({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide. It is white to off-white non hygroscopic powder. It may exist in several polymorphic forms. The structure was characterised using elemental analysis, IR, UV, 1H-NMR, 13C-NMR and MS.
The polymorphic form of the drug substance is Form I. Production of consistent polymorph has been confirmed by XRPD and stability of the polymorph was proven by both manufacturers.

The route of synthesis was sufficiently described by both manufacturers. Adequate specifications were set to control the quality of the starting materials, solvents, reagents and isolated intermediates.
Process impurities originating from the starting materials and the synthetic process were identified. Origin of each impurity was discussed.

The specification of rivaroxaban is acceptable in view of the route of synthesis and the European guidelines. Satisfactorily detailed descriptions and validations of the control methods were provided.

Batch analytical data demonstrating compliance with the drug substance specification have been provided. Control of the active substance has also been provided by finish product manufacturer. All results are within the limits of the specification.

The reference standards were adequately described and characterised.

Rivaroxaban is generally very stable at accelerated and long-term conditions and no specific degradational trends were observed.
The batches were stored in double PE bags placed in suitable drums. The proposed retest period and storage conditions have been justified by both manufacturers of API.

II.3 Medicinal Product

Pharmaceutical development
The aim of the product development was to produce a stable immediate-release oral dosage form (hard capsules) which displays satisfactory physical characteristics and bioequivalent to the reference product. The development of the product is described in sufficient detail. The choice of excipients is justified, and their function described. The results from comparative test between reference and proposed drug products have been provided.

Manufacture of the product
The drug product is manufactured by standard manufacturing process for this dosage form. The adequate information on manufacturing process, in-process controls, and critical steps was provided. The validation of the manufacturing process was performed on three batches manufactured for all strengths. The process produces finished product of consistent quality complying with the approved specification.

Product specification
The specifications based on relevant development and stability studies are generally considered acceptable for routine control of the drug product. The release and shelf life specifications include adequate tests to control physical, chemical and microbiological aspects of the product. Analytical methods are satisfactorily described and validated. The proposed parameters and their limits were justified.
Batch analytical data have been provided with API from both suppliers and the data demonstrated the compliance with the release specification. All batches met the test limits as defined in the release specification

Stability of the product
The capsules are packed in transparent PVC/PVdC//Al blisters and Al//Al (OPA/Al/PVC//Al) blisters as primary packaging material. These materials are conventional for solid dosage forms including hard capsules.
Stability studies were performed in line with the ICH stability guideline. Samples were stored at accelerated, intermediate, zone IVb and long-term conditions. The control tests and specifications for drug product are adequately drawn up.
Photostability and stress studies were provided. The results demonstrated that drug products are stable upon exposure to light.
There is no need to introduce any storage restrictions in the SmPC for Al/Al blisters.
The restriction ”Store below 30 °C. Store in the original package in order to protect from moisture.” was supported by stability data for PVC/PVdC//Al blisters.

In conclusion the stability results support the proposed shelf life of 2 years for commercially packed products under the conditions specified in the SmPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The quality of the drug product is adequately established. Satisfactory chemical and pharmaceutical documentation was submitted for marketing authorisation.
Information on development, manufacture, control of the drug substance and drug product, was satisfactorily presented. The results of tests indicate satisfactory consistency and uniformity of drug product characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of rivaroxaban are well known. As rivaroxaban is a widely used, well-known active substance, the Applicant did not provide additional studies and further studies were not required. Overview based on literature review was, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivaroxaban Zentiva and Xanirva were intended for generic indication, this would not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the pharmacokinetics, clinical efficacy and safety was adequate.
The proposed indications and posology were in line with the reference product.

IV.2 Pharmacokinetics

To support the application, the Applicant submitted three bioequivalence studies.

Clinical study I
This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study performed in 44 healthy, adult, non-smoking male and female subjects under fed conditions.

The objective of this study was to evaluate the comparative bioavailability between Rivaroxaban Capsules 10 mg and Xarelto 10 mg, film-coated tablets after a single-dose in healthy subjects under fasting conditions.

Results

Table 1. Pharmacokinetic parameters for Rivaroxaban (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (N=44)	1395.63 ± 372.28	1453.26 ± 368.30 *(considered N=43)*	170.54 ± 54.87	2.33 (0.67 – 4.00)
Reference (N=44)	1427.91 ± 385.20	1462.73 ± 393.37	184.56 ± 53.23	2.00 (0.67 – 4.00)
***Ratio (90% CI)**	97.88%	*Not calculated*	91.28%	

	(94.37%, 101.51%)		(86.99%, 95.79%)	
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t (t=48 hours) AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached				

ln-transformed values

Clinical study II

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study performed in 40 healthy, adult, non-smoking male and female subjects under fed conditions.

The objective of this study was to evaluate the comparative bioavailability between Rivaroxaban Capsules 20 mg, sprinkled on and mixed with applesauce, and Xarelto 20 mg, film-coated tablets, crushed and administered with applesauce after a single-dose in healthy subjects under fed conditions.

Results

Table 1. Pharmacokinetic parameters for Rivaroxaban (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (N=38)	2787.40 ± 658.95	2846.31 ± 645.98	248.39 ± 41.89	4.50 (1.00 – 12.00)
Reference (N=)	2611.97 ± 624.09	2689.86 ± 631.99	242.16 ± 48.91	4.25 (0.50 – 8.00)
***Ratio (90% CI)**	106.81% (103.36%, 110.37%)	106.01% (102.72%, 109.40%)	103.08% (97.98%, 108.45%)	
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t (t=48 hours) **AUC_{0-72h}** can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached				

ln-transformed values

Clinical study III

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study performed in 40 healthy, adult, non-smoking male and female subjects under fed conditions.

The objective of this study was to evaluate the comparative bioavailability between Rivaroxaban Capsules 20 mg and Xarelto 20 mg film-coated tablets after a single dose in healthy subjects under fed conditions.

Results

Table 1. Pharmacokinetic parameters for Rivaroxaban (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test (N=38)	3049.39 ± 709.04	3124.42 ± 701.53	354.13 ± 92.74	3.41 (1.23 – 33.60)
Reference (N=38)	2913.22 ± 885.68	2998.61 ± 864.62	376.11 ± 98.47	3.75 (0.50 – 6.00)
***Ratio (90% CI)**	106.62% (101.78%, 111.69%)	105.78% (101.44%, 110.31%)	94.22% (88.82%, 99.95%)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t (t=48 hours)
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

ln-transformed values

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Rivaroxaban 10 mg and 20 mg Capsules are considered bioequivalent with Xarelto 10 mg and 20 mg film-coated tablets.

The results of studies with 10 mg and 20 mg formulation can be extrapolated to other strengths 2.5 mg and 15 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan

The Applicant 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 Zentiva and Xanirva.

Summary table of safety concerns as approved in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal toxicity
Missing information	• Patients with severe renal impairment (creatinine clearance < 30 mL/min) • Remedial procoagulant therapy for excessive haemorrhage • 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) • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long term therapy with rivaroxaban in treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke prevention in patients with nonvalvular atrial fibrillation (SPAF) and acute coronary syndrome (ACS) in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients <18 years of age

Routine pharmacovigilance was suggested including specific follow-up questionnaires for liver-related adverse events, renal impairment/renal failure, severe hypersensitivity, and severe skin reactions was suggested. No additional pharmacovigilance activities were proposed by the Applicant, which was endorsed.

Following additional risk minimisation measures were considered necessary to minimise the risk of haemorrhage, which key elements are in line with those of the reference medicinal product.

The physician educational pack:
Educational materials will be circulated to physicians who may be involved in treating patients with rivaroxaban and is aimed to increase awareness about the potential risk of bleeding.

The patient alert card:
Educational materials will be provided to patients in each medication pack. Patients should show this card to every physician in order to reduce the risk of bleeding and provide them with information regarding INR. Patients are also informed to seek medical help if they experience any signs or symptoms of bleeding.

IV.4 Discussion on the clinical aspects

The applications contained an adequate review of published pre-clinical and clinical data. The bioequivalence between test and reference product has been shown under fast and fed conditions and the biowaiver for additional strengths was granted.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the applications for Rivaroxaban Zentiva and Xanirva, 2.5 mg, 10mg, 15 mg, 20mg, capsules, hard, were considered positive.

The bioequivalence between test and reference product has been shown under fast and fed conditions. The biowaiver for additional strengths was accepted.

The SmPC, PL and labelling are satisfactory.

Agreement between Member States was reached during the procedure. There was no discussion in the CMDh. The decentralised procedures were finalised with a positive outcome on 22nd March 2020.

A commitment regarding the replacing the colouring agent in capsule of 2.5 mg and 20 mg strengths via a type B.II.a.3.a.1 variation have been submitted.

Additional Risk Minimisation Measures including educational material have been agreed during the procedures:

The physician educational pack should contain:
• The Summary of Product Characteristics
• Prescriber Guide
• Patient Alert Cards

The MAH must agree the content and format of the educational material 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 hard capsules with food
• Management of overdose situations
• The use of coagulation tests and their interpretation
• That all patients should be counselled about:
    o Signs or symptoms of bleeding and when to seek attention from a health care provider
    o Importance of treatment compliance
    o The need for intake of the 15 mg and 20 mg hard capsules with food
    o Necessity to carry the Patient Alert Card that is included in each pack, with them at all
    times
    o The need to inform Health Care Professionals that they are taking rivaroxaban if they
    need to have any surgery or invasive procedure.

The Patient Alert Card should contain the following key safety messages:
• Signs or symptoms of bleeding and when to seek attention from health care provider
• Importance of treatment compliance
• The need for intake of the 15 mg and 20 mg hard capsules with food
• Necessity to carry the Patient alert card 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.