COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Runaplax 2.5 mg film-coated tablets

(rivaroxaban)

NL/H/3900/004/DC

Date: 25 March 2021

This module reflects the scientific discussion for the approval of Runaplax 2.5 mg film-coated tablets. The procedure was finalised on 25 November 2019. 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 Runaplax 2.5 mg film-coated tablets from Sandoz B.V.

The product, 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 SmPC sections 4.3, 4.4 and 5.1).

The product, 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.

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 film-coated tablets (NL License RVG 111484) which has been registered in the EEA by Bayer Pharma AG through centralised procedure EU/1/08/472/ since 22 May 2013.

This application concerns a line extension to the previously approved Runaplax 10 mg, 15 mg and 20 mg film-coated tablets (NL/H/3898/001-003/DC). The marketing authorisation was granted on 23 November 2017 in the Netherlands.

The concerned member states (CMS) involved in this procedure were Estonia, Lithuania, Latvia, Poland and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Runaplax 2.5 mg is a yellow coloured, round, biconvex film-coated tablet marked with '2.5' on one side. Each tablet contains 2.5 mg rivaroxaban.

The film-coated tablets are packed in:

- Transparent or opaque PVC/PVDC-Aluminium foil blister
- Transparent or opaque PVC/PVDC-Aluminium foil perforated unit dose blister
- HDPE tablet container with PP child resistant screw cap containing desiccant (silica gel)

The excipients are:
Tablet core - lactose monohydrate, sodium laurilsulphate (E487), hypromellose (substitution type 2910) (E464), croscarmellose sodium (E468), magnesium stearate (E470b), cellulose microcrystalline (E460), and silica colloidal anhydrous (E551).
film-coat – hypromellose (substitution type 2910) (E464), macrogol 3350 (E1521), titanium dioxide (E171), tartrazine aluminum lake (E102), indigo carmine aluminum lake (E132) and sunset yellow FCF aluminum lake (E110)

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.) at the time the procedure was closed. It is a white to off-white powder. Rivaroxaban is practically insoluble in aqueous solutions, and belongs to BCS class II. Micronized rivaroxaban is used due to poor solubility. 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 are acceptable. The chemical transformation steps that are used to form the final drug substance are appropriate.

Quality control of drug substance
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 this specification have been provided for two batches.

Stability of drug substance
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 observed (including polymorphic stability). Analytical results were obtained with stability indicating methods.

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.

A bioequivalence study have been submitted. The test product (2.5 mg) used in the bioequivalence study is acceptable in view of composition, manufacture and batch size.

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 in accordance with the relevant European guidelines.

Control of excipients

The excipients are tested according to their Ph.Eur. monographs. Specifications for the Opadry mixtures are provided. These specifications are acceptable.

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 covering 18 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 encephalo-pathies

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 Runaplax 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 Runaplax 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Runaplax 2.5 mg film-coated tablets (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Xarelto 2,5 mg film-coated tablets (Bayer AG, Germany).

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. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male/female subjects, aged 19-54 years. Each subject received a single dose (2.5 mg) of one of the 2 rivaroxaban formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 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 and 24 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting condition applied in the study is considered adequate.

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.

Results

One subject did not report to the facility for check-in for the second period and one subject due to very low plasma concentrations for the reference product. Therefore, 54 subjects were included in the pharmacokinetic analysis.

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

Treatment N=54	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	507 ± 120	523 ± 127	82 ± 22	2.33 (0.75 – 4.67)	4.5 ± 0.8

Reference	497 ± 122	509 ± 130	82 ± 19	2.0 (0.75 – 4.0)	4.3 ± 0.7
***Ratio (90% CI)**	1.02 (1.00-1.05)	--	0.98 (0.94 – 1.03)	--	--
CV (%)	8.1	--	13.6	--	--

$AUC_{0-\infty}$ 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 study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Runaplax 2.5 mg film-coated tablets is considered bioequivalent with Xarelto 2,5 mg film-coated tablets.

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 Runaplax.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-foetal toxicity
Missing information	• Safety in patients with severe renal impairment (creatinine clearance (CrCl) < 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 azoleantimycotics (e.g. ketoconazole) and Human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir) • Safety in pregnant or breast-feeding women • Safety in patients with atrial fibrillation (AF) secondary to significant heart disease and a prosthetic heart valve

	• Safety regarding long-term therapy with rivaroxaban in treatment of DVT, PE, stroke prevention in patients with non-valvular AF (SPAF) and ACS in real-life setting • Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Safety in patients < 18 years

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:

- The SmPC
- Patient alert cards
- 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 Runaplax 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.

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 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. 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

Runaplax 2.5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Xarelto 2.5 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 Runaplax with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 November 2020.

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