CBG MEB

Public Assessment Report

Scientific discussion

Runaplax 10 mg, 15 mg and 20 mg film-coated tablets

(rivaroxaban)

NL/H/3900/001-003/DC

Date: 21 August 2018

This module reflects the scientific discussion for the approval of Runaplax 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised on 1 September 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 Runaplax 10 mg, 15 mg and 20 mg film-coated tablets from Sandoz B.V.

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 (see SmPC section 4.4 for haemodynamically unstable PE patients).

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 10 mg, 15 mg, 20 mg film-coated tablets (NL License RVG 101535, 109000, 109002) which has been registered in the EEA by Bayer Pharma AG through centralised procedure EU/1/08/472/001-010 since 30 September 2008 (10 mg) and 9 December 2011 (15 mg and 20 mg).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Estonia, Croatia. Latvia, Lithuania, Poland, Romania 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 is a round biconvex film-coated tablet:
- The 10 mg strength is a peach coloured film-coated tablet marked with ‘10’ on one side.
- The 15 mg strength is a light orange coloured film-coated tablet marked with ‘15’ on one side.
- The 20 mg strength is an orange coloured film coated tablet marked with ‘20’ on one side.

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

The film-coated tablets are packed in:
- OPA/Aluminium/PVC/Aluminium foil blister
- OPA/Aluminium/PVC/Aluminium foil perforated unit dose blister
- 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 laurilsulfate, hypromellose, croscarmellose sodium, magnesium stearate, cellulose microcrystalline, and silica colloidal anhydrous.
10 mg film-coat – hypromellose, titanium dioxide (E171), macrogol, talc, sunset yellow FCF aluminium lake (E110), and iron oxide red (E172).
15 mg film-coat – hypromellose, titanium dioxide (E171), macrogol, sunset yellow FCF aluminium lake (E110), and iron oxide red (E172).
20 mg film-coat – hypromellose, titanium dioxide (E171), macrogol, sunset yellow FCF aluminium lake (E110), iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172).

The 15 mg and 20 mg tablet strengths are dose 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 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
Stability data on the active substance have been provided for 11 batches in accordance with applicable European guidelines. The active substance was stored for 60 months at 25°C/60% RH, for six months at 40°C/75% RH. No trends or changes were seen in any of the tested parameters at both storage conditions. Based on the data submitted, a retest period could be granted of 60 months with no special storage conditions.

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 optimization trials and comparative dissolution studies with the innovator product. *In vitro* studies have been performed to demonstrate similarity of the drug product and the reference product with respect to administration via nasogastric tube or gastric feeding tube. The results show that the test product and reference product are comparable with respect to the tested parameters. Hence, Rivaroxaban film-coated tablets can be administered via gastric tubes similar to the reference product. The SmPC text with respect to administration via gastric tube is similar to the reference product.

Two bioequivalence studies have been submitted. 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/ICH 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 Opadry Orange mixtures, are tested according to their Ph.Eur. monographs. Specifications for the Opadry Orange 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 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 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 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 Runaplax 10 mg and 20 mg film-coated tablets (Sandoz B.V., The Netherlands) 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
The MAH has requested a biowaiver for the 15 mg formulation based on the bioequivalence study with the 20 mg formulation. 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 15 mg 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.

This replicate-design study was analysed for scaled average bioequivalence approach. The bioequivalence acceptance criteria were based on intra-subject variability of reference product as follows:

- If the intra-subject CV for C_{max} parameter was >30% for reference product in the study, then the product was considered as highly variable and limit for bioequivalence for C_{max} was applied based on scaled average bioequivalence approach. However, in this case the point estimate (T/R) should fall between 80.00-125.00%.
- If the intra-subject CV for C_{max} parameter was <30% for reference product in the study, then conventional bioequivalence limit was considered for C_{max}. In that case, the test product was considered to be bioequivalent to the reference product if the 90% CI for the ratio of the geometric least square means of natural log transformed C_{max} of Test and Reference formulations fall within 80.00% to 125.00%.

In any case, the conventional average bioequivalence criteria using 90% CI was to be considered as 80.00% to 125.00% for AUC_{0-t}.

Bioequivalence study I – 10 mg strength under fasted conditions

Design

A randomised, balanced, open label, two treatment, four period, two sequence, single oral dose, crossover, fully replicate bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 22-44 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 four dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.66, 1.00, 1.50, 1.75, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.0, 4.5, 5, 6, 8, 12, 16 and 24 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

46 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=46	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1785 ± 391	1893 ± 415	252 ± 60	2.50 (1.00 – 5.00)
Reference	1611 ± 349	1754 ± 377	215 ± 57	2.33 (0.66 – 5.00)
***Ratio (90% CI)**	1.11 (1.07 – 1.15)	--	1.18 (1.12 – 1.24)	--
CV (%)	14.43	--	22.18	--

$AUC_{0-\infty}$	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

A randomised, balanced, open label, two treatment, two period, two sequence, single oral dose, crossover, fully replicate bioequivalence study was carried out under fed conditions in 18 healthy male subjects, aged 25-41 years. Each subject received a single dose (20 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. The high calorie high fat breakfast contained 42 gram proteins, 58.1 gram fat, 66.3 gram CHO and a total amount of calories of 956. The study used only two periods, instead of four. These periods were separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.00, 3.33, 4.0, 4.33, 4.66, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 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

18 subjects completed at least two periods 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=18	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	3576 ± 561	3639 ± 590	438 ± 53	4.2 (1.33 – 5.52)
Reference	3617 ± 629	3693 ± 645	415 ± 72	2.5 (1.33 – 5.50)
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	--	1.06 (1.00 – 1.13)	--

$AUC_{0-\infty}$ 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 Runaplax 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 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 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:

- 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 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.
- 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 in line with the contents of the alert card of the reference product.

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

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 10 mg, 15 mg and 20 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Xarelto 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 Runaplax with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 September 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