COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Xartil 10 mg, 15 mg and 20 mg film-coated tablets (rivaroxaban)

NL/H/5418/001-003/DC

Date: 25 April 2024

This module reflects the scientific discussion for the approval of Xartil 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised on 28 November 2023. 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
DTV	Deep Vein Thrombosis
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PE	Pulmonary Embolism
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VTE	Venous Thromboembolism

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Xartil 10 mg, 15 mg and 20 mg film-coated tablets, from GAP S.A.

Xartil has the following indications at different strengths:

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

The product is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults.

Xartil 15 mg
The product is 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.

The product is indicated for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

The product is 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.

Xartil 20 mg
The product is 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.

The product is indicated for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

The product indicated for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Xarelto 10 mg, 15 mg, 20 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EMEA/1/08/472-001) since 30 September 2008 by Bayer AG. The additional strengths (15 and 20 mg) were registered on 9 December 2011.

The concerned member state (CMS) involved in this procedure was Greece.

II. QUALITY ASPECTS

II.1 Introduction

Xartil 10 mg, 15 mg and 20 mg are film-coated tablets. Each film-coated tablet contains as active substance 10 mg, 15 mg or 20 mg rivaroxaban. The three strengths of the film-coated tablets can be distinguished by the colours and debossing and are as follows:

Xartil 10 mg
The 10 mg strength tablets are round, biconvex, pink, film coated, debossed with "L2" on one side.

Xartil 15 mg
The 15 mg strength tablets are round, biconvex, brown, film coated, debossed with "L3" on one side.

Xartil 20 mg
The 20 mg strength tablets are round, biconvex, dark red, film coated, debossed with "L7" on one side.

The excipients are:
Tablet core - microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose (2910), sodium laurilsulfate, and magnesium stearate.
Film-coat – macrogol, hypromellose (2910), titanium dioxide (E171), and red iron oxide (E172).

The 15 mg and 20 mg tablets are dose-proportional. The 15 mg and 20 mg tablet cores are quantitatively proportional. The 10 mg and 20 mg tablet cores have the same weight and only differ in the quantities of active substance and diluents

The film-coated tablets (all strengths) are packed in polyvinyl chloride/polyvinylidene chloride-aluminium (PVC/PVdC-Al) blisters in cartons.

II.2 Drug Substance

The active substance is rivaroxaban, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white powder,

practically insoluble in water. The active substance incorporates one stereogenic centre in its structure and is a pure enantiomer. Different polymorphic forms of rivaroxaban are known. The polymorphic form used is referred to as polymorphic form-I. An ASMF and CEP were submitted.

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.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional tests for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for five batches (two from manufacturer I and three from manufacturer II).

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference products, optimisation of the formulation and manufacturing process, dissolution method development and performance of comparative dissolution studies. Bioequivalence (BE) studies have been

performed for the 10 mg and 20 mg product versus their respective reference product strengths. The batches used in the BE studies were manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at 3 pH values has been successfully studied to support the bioequivalence study and the biowaiver for the 15 mg strength.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four pilot scaled batches per strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. The main steps of the manufacturing process are the blending of intragranular components, wet granulation, blending with extragranular components and lubrication, compression, film-coating and packaging. Process validation for full-scale batches will be performed post authorisation).

Control of excipients

The tablet core excipients comply with Ph.Eur. requirements and the ready-to-use film-coating materials comply with in-house requirements. Functionality-related characteristics of the tablet core excipients are controlled where relevant. 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 appearance, diameter, water, dissolution, uniformity of dosage units, identification, assay, related substances and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data four pilot scaled batches per strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from four production scaled batches of 10 mg and on four pilot scaled batches of the 15 mg and 20 mg strengths stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label. Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

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

Scientific data and/or certificates of suitability issued by the EDQM lactose monohydrate 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 Xartil 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 Xartil is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Xartil 10mg and 20mg (GAP S.A., Greece) was compared with the

pharmacokinetic profile of the reference product Xarelto 10 mg and 20 mg (Bayer AG, Germany).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution study results and composition. Comparative dissolution testing at pH 1.2 and 4.5 and 6.8 has been successfully studied in support of the bioequivalence study and the biowaiver for the 15 mg strength. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

The MAH has requested a biowaiver for the 15 mg formulation based on the bioequivalence study with the 20 mg formulation.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Rivaroxaban 10 mg may be taken with or without food since the oral bioavailability is high irrespective of fasting or fed conditions while the 15 mg and 20 mg tablets should be taken with food as it increases rivaroxaban mean AUC, as per EMA guidance Rev.3 EMA/CHMP/736403/2014, since there is a different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths, fasting study should be conducted for the lower strengths, and fed study for the higher strengths.

For patients unable to swallow the tablets whole, the tablets may be crushed and mixed with water or apple puree immediately prior to use and administered orally. The instructions on administration of the product through a nasogastric tube were verified as part of the development in comparison with the reference product. The pharmaceutical development of the product has been adequately performed.

Study 1 – rivaroxaban 10 mg, fasting conditions (whole tablet)

Design

A single centre, laboratory-blinded, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34

healthy male (14) and female (20) subjects, aged 22-55 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 a supervised overnight fast of at least 10 hours. Fasting continued for at least 4 hours following drug administration. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 16, 24, 36, and 48 hours after administration of the products.

The design of the study is acceptable.

Results
34 subjects enrolled in the study. One subject withdrew from the study due to personal reasons. 33 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 10mg under fasted conditions (whole tablet).

Treatment N=33	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1538.76	1582.68	201.87	2.0 (1.0-5.0)
Reference	1572.26	1618.96	206.60	2.0 (1.0-5.0)
***Ratio (90% CI)**	0.96 (0.91 – 1.02)	-	0.97 (0.88 – 1.06)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – rivaroxaban 10mg, fasted conditions (crushed tablet)
Design
A single centre, laboratory-blinded, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 33 healthy male (11) and female (22) subjects, aged 23-53 years. Each subject received a single dose (10 mg) of one of the two rivaroxaban formulations. The tablet was crushed and mixed with 40 mL of unsweetened apple puree. It orally administered with a total of ± 240 mL water after fasting overnight for at least 10 hours. Fasting continued for at least 4 hours following drug administration. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Results
34 subjects enrolled in the study. One subject withdrew consent from the study. 33 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=33	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1645.48	1676.08	205.73	2.5 (1.5-4.0)
Reference	1567.81	1600.45	198.32	2.0 (0.5-4.0)
***Ratio (90% CI)**	1.06 (0.99- 1.13)	-	1.04. (0.97 – 1.12)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3 – rivaroxaban 20 mg, fed conditions
Design
A single centre, laboratory-blinded, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 34 healthy male (17) and female (17) subjects, aged 20-55 years. Each subject received a single dose (20 mg) of one of the two rivaroxaban formulations. After a supervised overnight fast of at least 10 hours, subjects received a standardised high-fat, high-calorie meal (144 kcal protein, 531 kcal fat, 336 kcal carbohydrates) 30 minutes before drug administration. The tablet was orally administered with ± 240 mL water after. Subjects fasted for at least 4 hours following drug administration. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36, and 48 hours after administration of the products.

The design of the study is acceptable.

Results
34 subjects enrolled in the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rivaroxaban, 20mg 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	2893.45	2938.63	363.64	3.25 (1.00-5.00)
Reference	2841.76	2876.64	363.46	3.50 (1.00-6.00)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	-	0.99 (0.92 – 1.07)	-

$AUC_{0-\infty}$	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 = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Analytical/statistical methods
For all three studies, 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.

Conclusion on bioequivalence studies (study 1-3):
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 Xartil 10mg and 20mg are considered bioequivalent with Xarelto 10 mg and 20 mg.

The results of study 3 with the 20 mg formulation can be extrapolated to strength 15 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Xartil.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	Haemorrhage
Important potential risks	Embryo-foetal toxicity
Missing information	Remedial pro-coagulant therapy for excessive haemorrhage Patients with atrial fibrillation (AF) and prosthetic heart valve

At the time of approval of this product, it was considered that additional risk minimisation measures (including educational material) were necessary for the safe and effective use of the product. The educational material should be submitted by the MAH to the competent authorities of the Member States and its content and implementation should be agreed with the competent authorities prior to launch.

The educational material should contain the following key elements:

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk.

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 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 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 rivaroxaban if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in the product 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. The MAH demonstrated through three 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 package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Spanish.

The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Xartil 10mg, 15mg and 20mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xarelto 10 mg, 15 mg and 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 Xartil with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 November 2023.

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
-	-	-	-	-	-