COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ticagrelor Xiromed 60 mg and 90 mg film-coated tablets (ticagrelor)

NL/H/5716/001-002/DC

Date: 1 May 2025

This module reflects the scientific discussion for the approval of Ticagrelor Xiromed 60 mg and 90 mg film-coated tablets. The procedure was finalised on 7 February 2024. 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
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
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ticagrelor 60 mg and 90 mg film-coated tablets, from Medical Valley Invest AB.

The product, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with:

- acute coronary syndromes (ACS) or
- a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event

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 Brilique 60 mg and 90 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/10/655) since 3 December 2010.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Iceland, Norway, Poland and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Ticagrelor Xiromed 60 mg and 90 mg are film-coated tablets. The two strengths of the film-coated tablets can be distinguished by the size and the colour and are as follows:

Ticagrelor Xiromed 60 mg
The 60 mg tablets contain 60 mg ticagrelor as active substance and are round (diameter 8 mm), biconvex, pink coloured film-coated tablets, debossed with "I" on one side and plain on the other side.

Ticagrelor Xiromed 90 mg
The 90 mg tablets contain 90 mg ticagrelor as active substance and are round (diameter 9 mm), biconvex, yellow coloured film-coated tablets, debossed with "T" on one side and plain on the other side.

The excipients are:
Tablet core: cellulose microcrystalline (E460), mannitol (E421), crospovidone (E1202), povidone K30 (E1201), sodium starch glycolate (Type A), silica colloidal anhydrous (E551), and magnesium stearate (E470b).

Tablet coating: hypromellose (E464), titanium dioxide (E171), macrogol (E1521), iron oxide red (E172; only for the 60 mg strength), black iron oxide (E172; only for the 60 mg strength), talc (E553b; only for 90 mg strength), and iron oxide yellow (E172; only for 90 mg strength).

The two tablet cores are dose proportional.

The film-coated tablets are either packed in polyvinyl chloride-polyvinylidene dichloride (PVC-PVDC) transparent – aluminium blisters or packed in high-density polyethylene (HDPE) bottles with silica gel desiccant contained in the cap.

II.2 Drug Substance

The active substance is ticagrelor, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white, or almost white to pale pink, crystalline powder isolated in form-II, and is freely soluble in methanol, soluble in anhydrous ethanol, and practically insoluble in water and heptane. The active substance exhibits stereoisomerism and contains six chiral centres. For this product, polymorphic form-II is consistently produced and adequately controlled in the drug substance specification.

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 manufacturing process consists of eight steps from three starting materials. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

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. and the ASMF, with additional requirements for particle size distribution (PSD) and microbial limits. The manufacturer has adopted the Ph.Eur. method for the determination of impurities. The suitability of the analytical method and limits are adequately demonstrated and are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for six commercial scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated 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 choices of the packaging and manufacturing process are justified in relation to the innovator. Based on *in-vitro* feeding-tube studies, it has been demonstrated that as recommended in the SmPC, the film-coated tablets may be crushed and administered through a PVC and PUR nasogastric tube of a size CH8 or larger. Furthermore, based on a risk-based approach, the silicone tube can also be used for the administration of the proposed product.

Data shows that the polymorphic form of ticagrelor does not change during manufacturing. The QC dissolution method is based on the Ph.Eur. medicinal product monograph for ticagrelor tablets and discriminatory power was sufficiently demonstrated. A bioequivalence (BE) study was performed with the 90 mg product strength. For the 60 mg product a biowaiver is requested. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured by a standard wet granulation 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 of common blend and three minimum scale batches for each strength. Bulk stability studies were performed, the proposed bulk holding time is considered justified. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. 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, identification, average weight, water content, uniformity of dosage units, assay, dissolution, related substances and microbial control. Release and shelf-life limits are identical, except for water content and total impurities. 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. A low risk for presence of nitrosamines in the drug product was identified. the relevant nitrosamine impurity cannot be synthesized despite extensive efforts, this could be an indication that the nitrosamine either does not exist or that there is no risk of it being formed according to the EMA Q&A for marketing authorisation holders/applicants on the

CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products EMA/409815/2020 – Question 14 – and the provided risk evaluation supports this statement. Therefore, the provided nitrosamine risk evaluation is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three minimum scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three minimum scaled batches for each strength stored at 25°C/ 60% RH (9 - 24 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 2 years. No specific storage conditions needed to be included in the SmPC or on the label.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The post-approval commitment to perform manufacturing process validation for full-scale batches was made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ticagrelor Xiromed 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 Brilique 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

Ticagrelor 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ticagrelor Xiromed 90 mg film-coated tablets (Medical Valley Invest AB, Sweden) was compared with the pharmacokinetic profile of the reference product Brilique 90 mg film-coated tablets (AstraZeneca AB, Sweden).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

For the lower strength, Ticagrelor Xiromed 60 mg film-coated tablets, a biowaiver was granted because the following requirements were met, in accordance with 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 dissolution profiles of a Ticagrelor Xiromed 90 mg bio-batch was compared to three Ticagrelor

Xiromed 60 mg batches. Due to not meeting the conditions, a f_2 calculation was unsuitable, as well as alternative methods to f_2 calculations. Visual comparison of the trend observed in the dissolution profiles of the strengths of the test products (60 mg and 90 mg) is acceptable. The dissolution of the bio-batch and the 60 mg strength differ less than 10% at all required pH (pH 1.2, pH 4.5, and pH 6.8), showing that the trends are the same. Together with all provided data it can be concluded that the two strengths are similar. The biowaiver of strength is therefore acceptable.

Bioequivalence studies

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male (35) and female (9) subjects, aged 19-44 years. Each subject received a single dose (90 mg) of one of the two ticagrelor formulations. The tablet was orally administered with 240 ± 02 mL water after an overnight fasting of at least 10 hours. There were two dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.
The design of the study is acceptable.

Ticagrelor may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ticagrelor. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Two subjects were withdrawn from the study, one due to protocol violation (positive drug test) and the other due to a mild adverse event (vomiting, possibly related to the test product). 42 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ticagrelor, 90 mg under fasted conditions.

Treatment N=42	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	4693 ± 1615	4889 ± 1757	570 ± 168	2.67 (1.33 – 5.01)
Reference	4854 ± 1859	5042 ± 2008	623 ± 171	2.00 (1.00 – 4.00)

***Ratio (90% CI)**	0.98 (0.93 – 1.03)	-	0.91 (0.86 – 0.97)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs; presented as Median (Range)
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
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 study Ticagrelor Xiromed 90 mg is considered bioequivalent with Brilique 90 mg.

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 (version 0.2, signed 18 April 2023), 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 Ticagrelor Xiromed.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	Increased risk of bleeding
Important potential risks	None
Missing information	Long-term use in patients with prior ischaemic stroke

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Brilique. 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

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 test consisted of: a pilot test with 2 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

Ticagrelor Xiromed 60 mg and 90 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Brilique 60 mg and 90 mg film-coated tablets. Brilique 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 Ticagrelor Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 February 2024.

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
NL/H/5716/001-2/P/001	Art.61(3): Changes proposed in Annex IIIA (Label) and Annex IIIB (Package Leaflet)	Yes	15 April 2024	Approved	N.A.
NL/H/5716/001-2/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product: Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	4 February 2025	Approved	N.A.