COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5617/001-002/DC

Date: 19 November 2024

This module reflects the scientific discussion for the approval of Ticagrelor Macleods 60 mg and 90 mg film-coated tablets. The procedure was finalised on 6 December 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
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 Macleods 60 mg and 90 mg film-coated tablets, from Macleods Pharma Espana S.L.U.

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 state (CMS) involved in this procedure was Germany.

II. QUALITY ASPECTS

II.1 Introduction

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

Ticagrelor Macleods 60 mg
The 60 mg tablets contain 60 mg ticagrelor as active substance and are pink coloured, round, biconvex, film-coated tablets debossed“F35" on one side and plain on other side.

Ticagrelor Macleods 90 mg
The 90 mg tablets contain 90 mg ticagrelor as active substance and are yellow coloured, round, biconvex, film-coated tablets debossed “F37" on one side and plain on other side.

The excipients are:
Tablet core: mannitol (E421), cellulose microcrystalline (E460(i)), sodium starch glycolate (type A), povidone (E1201) and magnesium stearate (E572).
Tablet coating: hypromellose 6 cPs (E464), polyethylene glycol 400 (E1521), talc (E553b), titanium dioxide (E171), black iron oxide (E172; only for 60 mg strength), red iron oxide (E172; only for 60 mg strength) and yellow iron oxide (E172; only for 90 mg strength).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride-polyvinylidene dichloride/aluminium (PVC-PVDC/Al) blisters (with sun/moon symbols).

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 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 isomerism and contains six chiral centres. For this product, polymorphic form-II is consistently produced.

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 synthesising ticagrelor in four reaction steps. 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., with additional tests for polymorphic form, residual solvents and nitrosamines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Batch analytical data demonstrating compliance with the pre-Ph.Eur drug substance specification has been provided for three pilot scaled batches. Stability data on the active substance have been provided for three scaled-up batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 12 months. Based on the data submitted, a retest period could be granted of 60 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. A bioequivalence (BE) study was performed with the 90 mg product strength. For the 60 mg product a biowaiver is shown. The dissolution method has been adopted from the Ph.Eur, and a limit has been set accordingly.

Manufacturing process

The product is manufactured by wet granulation through the following steps: sifting, dry mixing, binder preparation, granulation, wet milling, drying, sifting and milling, lubrication, compression, film-coating, inspection, and packing. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients in the core tablets comply with Ph.Eur and in-house requirements, as well as relevant EC directives. 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 (of the active and colourants), water determination, dissolution, uniformity of dosage units, related substances, and assay. 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 from two batches for each 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 two batches for each strength stored at 25°C/ 60% RH (48 months and 60 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.

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 Macleods 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 Ticagrelor Macleods 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 Macleods 90 mg film-coated tablets (Macleods Pharma Espana S.L.U, Spain) 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 60 mg strength, 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. A biowaiver for the additional 60 mg strength is acceptable as dissolution similarity at all required pH (pH 1.2, pH 4.5, and pH 6.8) has been demonstrated.

Bioequivalence studies

Design

A single-dose, randomised, open-label, balanced, analyst blind, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-43 years. Each subject received a single dose (90 mg) of one of the two ticagrelor formulations. The tablet was orally administered with 240 mL water after 10 hours of overnight fasting. There were two 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, 3.5, 4, 4.5, 5, 6, 8, 12, 18, 24, 30, 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 due to adverse events (one subject had complaints of 1 episode of vomiting with blood tinged, epigastric bruning since 15-20 minutes and headache on day 2 of period 1 (post dose); and one subject had increased INR value in period 2 (pre-dose)). The remaining 22 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=22	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	6394.31 ± 1870.13	6552.54 ± 1959.38	816.43 ± 211.40	2.00 (1.00 - 4.00)
Reference	6245.55 ± 1614.32	6410.85 ± 1693.18	840.07 ± 195.16	2.00 (1.00 - 4.00)
***Ratio (90% CI)**	1.01 (0.95 - 1.06)	-	0.96 (0.87 - 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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 Ticagrelor Macleods 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, 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 Macleods.

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) for Ticagrelor Macleods 90 mg 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 English.
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.

A user consultation with target patient groups on the package leaflet (PL) for Ticagrelor Macleods 60 mg has been performed on the basis of a bridging report making reference to Ticagrelor Macleods 90 mg. 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

Ticagrelor Macleods 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 Macleods with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 December 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
NL/H/5617/001-2/IA/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmP CSmPC - Implementation of wording agreed by the competent authority	Yes	26 June 2024	Approved	N/A
NL/H/5617/IB/002/G	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process Replacement or addition of a	No	28 June 2024	Approved	N/A

	manufacturing site for part or all of the manufacturing process of the finished product – a. Secondary packaging site b. Primary packaging site e. Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.				