COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ticagrelor Mylan 60 mg and 90 mg, film-coated tablets

(ticagrelor)

NL/H/4815/001-002/DC

Date: 18 March 2021

This module reflects the scientific discussion for the approval of Ticagrelor Mylan 60 mg and 90 mg, film-coated tablets. The procedure was finalised at 20 November 2020. 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
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 Ticagrelor Mylan 60 mg and 90 mg, film-coated tablets, from Mylan B.V.

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 (see SmPC sections 4.2 and 5.1).

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 products Brilique 60 mg and 90 mg, film-coated tablets which have been registered in the EEA by AstraZeneca AB since 18 February 2016 and 3 December 2010 respectively via a centralised procedure (EU/1/10/655).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia (only the 90 mg strength), Finland, France (only the 90 mg strength), Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Latvia (only the 90 mg strength), Norway, Portugal, Spain and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Ticagrelor Mylan 60 mg is a round, biconvex, pink tablets marked with ‘60’ on one side and plain on the other. Each film-coated tablet contains 60 mg ticagrelor.
Ticagrelor Mylan 90 mg is round, biconvex, yellow tablets marked with ‘90’ on one side and plain on the other. Each film-coated tablet contains 90 mg ticagrelor.

The film-coated tablets are packed in Aluminium-OPA/Alu/PVC or Aluminium-PVC/PE/PVDC calendar blisters or High Density Polyethylene (HDPE) bottles closed with a polypropylene (PP) child resistant closure.

The excipients are:
Tablet core - mannitol (E421), calcium hydrogen phosphate dihydrate, maize starch, pregelatinised starch (maize), talc (E553b) and sodium stearyl fumarate
Tablet coating - poly (vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), glycerol monocaprylocaprate and sodium laurilsulfate. Only the 60 mg strength contains iron oxide red and black (E172) and the 90 mg strength contains iron oxide yellow (E172).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is ticagrelor, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.) or any other pharmacopoeia. Ticagrelor is a white to off-white crystalline powder and is freely soluble in methanol and acetone, soluble in ethyl acetate and practically insoluble in water. Ticagrelor contains six chiral centres and herewith exhibits isomerism. Crystalline form II of the active substance is manufactured.

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 a six-step synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. No class 1 solvents are used. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification compromises test for appearance, identification, specific optical rotation, loss on drying, residue on ignition, isomers, related substances, residual solvents, and assay and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. The ASMF holder claims retest period for 24 months. Based on the provided data the applied retest period of 24 months, with storage condition 'Preserve in tight containers, protect from light. Store at temperature not exceeds 25°C(77°F); excursions permitted between 15°C(59°F) and 30°C(86°F)' is acceptable

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 feasibility of administration via the nasogastric tube has been demonstrated. The MAH has performed a dose recovery-, an in-use stability-, a sedimentation volume- and a particle size distribution study. In view of the poor solubility of ticagrelor the particle size distribution a three tier limit is set for the particle size distribution. The enantiomeric form of the drug substance in the proposed drug product is the same as present in the reference product. The application is supported by one pilot and two pivotal bioequivalence studies with the 90 mg tablet of the drug product. In the pilot bioequivalence study, batches manufactured with two different PSD ticagrelor were compared with the reference product. All batches tested were found to be bioequivalent with the reference product. The QC dissolution method was optimised in compliance with the data from the bioequivalence studies. A biowaiver is proposed for the lower strength. The submitted dissolution data support the proposed biowaiver of the 60 mg strength. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process is a straightforward, standard wet granulation process and has been validated according to relevant European guidelines. Process validation data on the product have been presented for full-scaled batches in accordance with the relevant European guidelines.

Control of excipients

Where applicable, the excipients comply with Ph Eur. requirements. For iron oxide reference is made to the EU Regulation. 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, identification of active substance and colorants, uniformity of mass, dimensions, uniformity of dosage, related substances, dissolution, assay and microbial purity. 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 six production scaled batches (three 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 for three production scale blends stored at 25°C/60%RH (18 months) and 40°C/75%RH (6 months). As the two strengths are dose-proportional, the submission of data from three production scale blend batches is considered sufficient. All results comply. Trends are not observed. Based on the data proved

the claimed stability of 24 months is considered acceptable. The tablets are photostable. In the forced degradation studies, high moisture conditions had no effect on the quality of the finished product. Hence a dedicated in-use stability studies is not required

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 Mylan 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 Mylan 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 Brilique 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

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 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

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Ticagrelor Mylan 90 mg, film-coated tablets (Mylan B.V., the Netherlands) is 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 results with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver is requested for the 60 mg strength. The 60 mg and 90 mg strengths are dose proportional and manufactured by the same manufacturing process. The MAH has provided comparative dissolution profiles between Ticagrelor Mylan 90 mg film-coated tablets and Ticagrelor Mylan 60 mg film-coated tablets using paddle apparatus with 50 rpm in pH 1.2 (0.1 N HCl), pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Similarity has been shown between the 90 mg film-coated tablet and 60 mg film-coated tablet at all three pH levels. All conditions for biowaiver of strengths have been fulfilled and a biowaiver for 60 mg film-coated tablets can be granted.

Bioequivalence studies

Bioequivalence study I

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 27-65 years. Each subject received a single dose (90 mg) of one of the 2 ticagrelor 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 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36 and 48 after administration of the products.

The design of the study is acceptable. A single dose, crossover study under fasting conditions 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
All 30 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=30	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	2883 ± 1155	2990 ± 1179	538 ± 186	1.67 (1.0-6.0)	7.6 ± 1.6
Reference	2557 ± 916	2675 ± 933	462 ± 151	2.0 (1.0-4.0)	7.7 ± 1.9
***Ratio (90% CI)**	1.11 (1.06 – 1.16)	--	1.16 (1.05 – 1.27)	--	--
CV (%)	10.5	--	21.1	--	--

$AUC_{0-\infty}$ 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
This study failed to show bioequivalence for C_{max}. A new pivotal study (bioequivalence study II) was carried out with a reference batch not close to its expiry date and including more subjects.

Bioequivalence study II
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 18-44 years. Each subject received a single dose (90 mg) of one of the 2 ticagrelor 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 0.33, 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. A single dose, crossover study under fasting conditions 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 was withdrawn from the study because of misbehaviour, one because he had a positive alcohol breath test, one due to vomiting and one due to an adverse event. Therefore, 60 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=60	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	5305 ± 1568	5389 ± 1615	692 ± 214	2.0 (1.0-4.0)	7.5 ± 1.2
Reference	5307 ± 1352	5389 ± 1389	694 ± 183	1.67 (1.0-5.0)	7.6 ± 1.3
***Ratio (90% CI)**	1.00 (0.96-1.04)	--	0.99 (0.94-1.04)	--	--
CV (%)	11.7	--	17.5	--	--

$AUC_{0-\infty}$ 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*

Pooled analysis
A pooled analysis was carried out on the two pivotal studies. This pooled analysis showed bioequivalence for AUC_{0-t} (ratio 1.04, 90% CI 1.01 - 1.07) and for C_{max} (ratio 1.04, 90% CI 0.99 - 1.10).

Additional analysis
It was noted that 5 subjects were excluded from the analysis as they had missed ambulatory samples during the study. A statistical analysis was requested including these 5 subjects. The results of the analysis are presented below. In addition, the MAH also provided a statistical analysis for the pooled data including the 5 excluded subjects. Bioequivalence could still be proven in both cases.

Table 3. The statistical results for the pharmacokinetic parameters C_{max} and AUC_{0-t} of ticagrelor (including the five subjects).

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 60)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ng/mL)	663.454	670.306	98.98	17.53	93.86% - 104.38%	100.00
AUC_{0-t} (hr*ng/mL)	5067.651	5065.662	100.04	11.55	96.58% - 103.62%	100.00

Table 4. The statistical pooled analyses results for the pharmacokinetic parameters C_{max} and AUC_{0-t} of ticagrelor (including the five subjects).

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N=60)			Intra subject %CV	90% CI	Results
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ng/mL)	605.860	580.638	104.34	20.12	99.32% - 109.62%	Bioequivalence Meet
AUC_{0-t} (hr*ng / mL)	4103.110	3957.497	103.68	12.34	100.57%- 106.89%	Bioequivalence Meet

Conclusion on bioequivalence studies

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 studies Ticagrelor Mylan is considered bioequivalent with Brilique.

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 Mylan.

Table 5. 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

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 Brilique 60 mg and 90 mg, film-coated tablets. 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 Mylan 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 Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 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