*CMDh/223/2005*
*February 2014*

# Public Assessment Report

# Scientific discussion

# Ticagrelor HCS-BV 60 mg and 90 mg film-coated tablets, Atirabo 60 mg and 90 mg film-coated tablets

# (Ticagrelor)

# HU/H/0866-0867/001-002/DC

# Date: 04/07/2025

**This module reflects the scientific discussion for the approval of Ticagrelor HCS-BV 60 mg and 90 mg film-coated tablets, Atirabo 60 mg and 90 mg film-coated tablets. The procedure was finalised on 29.01.2024. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ticagrelor HCS-BV 60 mg and 90 mg film-coated tablets, 60 mg and 90 mg film-coated tablets

The product is approved for the following indications:
the prevention of atherothrombotic events (co-administered with acetylsalicylic acid (ASA)) 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Brilique 60mg and 90 mg film-coated tablet which have been registered in the EEA by Astra Zeneca AB since 03/12/2010 through centralised procedure EU/1/10/655.

The concerned member states (CMS) involved in this procedure were HU/H/0866 Germany; HU/H/0867 Czechia, Estonia, Latvia, Lithuania, Poland, Slovakia.

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

# II. QUALITY ASPECTS

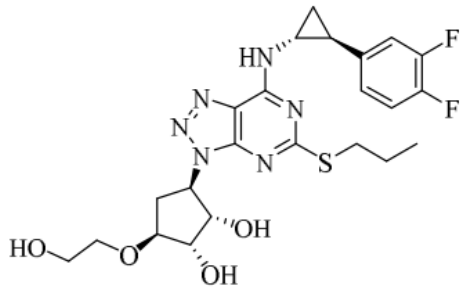
## II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Ticagrelor 60 mg and 90 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. generic application).
Reference products are Brilique 60 mg and 90 mg film-coated tablets (containing 60 mg and 90 mg ticagrelor as active ingredient, respectively) which were the original products of Astra Zeneca AB.

## II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (EU - ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Ticagrelor
Chemical name: (1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol
Structure:



The active substance is white to almost white or to pale pink or to brownish white powder. Ticagrelor is freely soluble in methanol, sparingly soluble in ethyl acetate, and practically insoluble in water and heptane. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by $^{1}$H- and $^{13}$C-NMR, FT-IR and MS spectroscopy, elemental analysis (CHN), specific optical rotation and X-Ray powder diffraction spectra (for polymorphic form). The impurity profile of the API contains detailed information about organic impurities, residual solvents and catalysts. The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Ticagrelor is official in the Ph.Eur., in-house specification had been set for the active substance. The in-house specification includes the following tests: identification, loss on drying, sulphated ash, specific optical rotation, related substances, assay, residual solvents, particle size and microbiological quality.
The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable when the API is stored in the original packaging material in order to protect from light.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

## II.3 Medicinal Product

The aim was to develop film-coated tablets containing Ticagrelor as drug substance in 60 mg and 90 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product Brillique® 60 mg and 90 mg film-coated tablets, the branded original products of AstraZeneca AB.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.

*60 mg strength:* Light pink, round, biconvex, film-coated tablets marked with 60 on one side. Tablet dimensions: approximately 8 mm diameter.
*90 mg strength:* Slightly brownish-yellow, round, biconvex, film-coated tablets marked with 90 on one side. Tablet dimensions: approximately 9 mm diameter.
The excipients used in the finished product are microcrystalline cellulose, calcium hydrogen phosphate dihydrate, hypromellose 2910, croscarmellose sodium, magnesium stearate and ready-to-use film-coating (hypromellose, titanium dioxide (E171), talc, propylene glycol, yellow iron oxide (E172) – *only for 90 mg* or red and black iron oxide (E172) – *only for 60 mg).*
All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur., the ICH Q6A guideline, as well as the Ph. Eur. monograph of Ticagrelor tablets. Appropriate control strategy was selected. The test methods have been described and adequately validated. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is Aluminum-PVC/PVDC blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 3 years with no special storage conditions** is approved.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

*Conclusion:* The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ticagrelor HCS-BV 60 mg and 90 mg film-coated tablets, Atirabo 60 mg and 90 mg film-coated tablets are 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 one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

The pharmacokinetic profile of ticagrelor has been evaluated in healthy volunteers and in patients with CAD, atherosclerosis and ACS. The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI were generally similar to that in the ACS population.
Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.
Administration of ticagrelor 200 mg (once daily or twice daily) with food had no apparent effect on exposure to AR-C124910XX compared with fasting administration; therefore, ticagrelor can be given with or without food.

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, for immediate release products claiming essential similarity to the reference product, a bioequivalence study is required to support the application.

To support the application, the applicant has submitted one pivotal bioequivalence study for the strength 90 mg. The pivotal study is a single center, randomized, single-dose, open-label, 2-way crossover BE study to compare the rate and extent of absorption of a test Ticagrelor 90 mg film-coated tablet versus Brilique® (AstraZeneca AB, Sweden, EU), a reference Ticagrelor 90 mg film-coated tablet, under fasting conditions.

*Results*

**Pharmacokinetic parameters for Ticagrelor (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) N=35 subjects (Study No. 18-609)**

| Treatment | $AUC_{0-t}$ ng/ml/h | $AUC_{0-\infty}$ ng/ml/h | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | 3147.49 (±969.08) | 3257.58 (±1007.06) | 565.34 (±231.35) | 2.018 (0.987, 5.991) |
| **Reference** | 3019.33 (±1008.72) | 3108.60 (±1032.35) | 512.95 (±184.19) | 1.736 (0.988, 5.989) |
| ***Ratio (90% CI)** | 105.30% (101.49%-109.25%) | 105.69% 101.93% - 109.59%) | 108.33% (100.03%-117.32%) | - |
| **$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t. | | | | |

| | |
|---|---|
| | $AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products |
| **$AUC_{0-\infty}$** | Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$ |
| **$C_{max}$** | Maximum plasma concentration |
| **$t_{max}$** | Time until Cmax is reached |

**ln-transformed values*

*Conclusion*
Based on the submitted bioequivalence study Test Product (Ticagrelor 90 mg film-coated tablets,) is considered bioequivalent with Reference Product (Brilique® 90 mg film-coated tablets, AstraZeneca AB, Sweden, EU) under fasting conditions.

Biowaiver

The MAH requested a biowaiver for the 60 mg strength based on the bioequivalence study performed with the 90 mg tablet.
According to all dissolution results and the fact that in all tested media, Ticagrelor 90 mg film-coated tablets show similar dissolution behaviour with Ticagrelor 60 mg film-coated tablets, the requirements in regard to in vitro comparisons for biowaiver of Ticagrelor film-coated tablets, are fulfilled according to 4.1.6 Guide CPMP/EWP/QWP/1401/98 Rev. 1/Corr**.

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study Test Product (Ticagrelor 90 mg film-coated tablets) is considered bioequivalent with Reference Product (Brilique® 90 mg film-coated tablets, AstraZeneca AB, Sweden, EU) under fasting conditions.
The results of the bioequivalence studies with the 90 mg formulation can be extrapolated to the 60 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

## IV.3 Summary of Pharmacovigilance System

The KRKA has submitted a signed Summary of Pharmacovigilance Systems covering the proposed MAHs dated on 20.10.2021:

For HCS bvba Belgium and 123 Acurae Pharma GmbH Germany, which are the MAHs in HU and in DE respectively in HU/H/0866/001-002/DC

For KRKA, which is MAH in CZ, EE, LT, LV, PL, SK and HU in HU/H/0867/001-002/DC

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

## IV.4 Risk Management Plan (version number: 1.1 signed 29.01.2024)

### 1.1 Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | None |

| Summary of safety concerns | |
|---|---|
| **Important potential risks** | None |
| **Missing information** | None |

The safety concerns listed by the MAH are appropriate, since it is in line with the latest version of the reference product's RMP (Brillique film-60 mg, 90 mg film-coated tablets Astra Zeneca, Version number 11; Date of final sign off: 01 November 2018).

### IV.5 Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to products containing ticagrelor.

No additional activities are proposed.

### IV.6 Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to products containing ticagrelor.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

### IV.7 PSUR

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

### IV.8 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 information leaflet (PIL) has been performed on the basis of a bridging report making reference to Maruxa 10 mg, 20 mg film-coated tablets and Brilique, 60 mg, film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

**Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC**

None.

**Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC**

- **Additional risk minimisation measures (including educational material)**

None.

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83**

None.

- **Specific obligation to complete post-authorisation measures for <the marketing authorisation under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

None.