

Public Assessment Report

Scientific discussion

Auretica
(ticagrelor)

SE/H/2377/01-02/DC

This module reflects the scientific discussion for the approval of Auretica. The procedure was finalised on 2024-03-20. 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, a marketing authorisation has been granted for Aretica, 60 mg, 90 mg, Film-coated tablet.

The active substance is ticagrelor. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Aretica, 60 mg, 90 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as the sole concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Brilique, 60 mg, Film-coated tablet Centrally authorised in the European Union since 2010, with AstraZeneca AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Brilique, 90 mg, Film-coated tablet from Greece with AstraZeneca AB as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of ticagrelor are well known. As ticagrelor is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Aurette is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Aurette from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Aurette (Ticagrelor) with the reference product Brilique.

Pharmacokinetic properties of the active substance

Absorption: The mean absolute bioavailability of ticagrelor was estimated to be 36%. Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours.

Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food.

Linearity: Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite are approximately dose proportional up to 1260 mg.

Elimination: The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Study TICA22018

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (34 completed), comparing Ticagrelor, 90 mg, film-coated tablet with Brilique, 90 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of ticagrelor were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 2022-05-15 and 2022-05-23.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for ticagrelor, n=34.

Treatment	AUC _{0-t} ng*h/ml	C _{max} ng/ml	t _{max} h
Test	3153.483 $\pm$ 1236.551	538.789 $\pm$ 210.137	1.67 (1.00-4.00)
Reference	3364.362 $\pm$ 1409.631	580.561 $\pm$ 195.085	1.67 (1.00-3.00)
*Ratio (90% CI)	95.28 (90.92-99.84)	90.78 (85.02-96.94)	-
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 plasma concentration			

*calculated based on ln-transformed data

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 60 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and the EMA Ticagrelor film-coated tablets 60 mg and 90 mg product-specific bioequivalence guidance (EMA/CHMP/177281/2016/Corr.[†]). The bioanalytical method was adequately validated.

Absence of studies with the additional strength of 60 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) are fulfilled and since the pharmacokinetics of ticagrelor is linear between 60 mg and 90 mg.

Based on the submitted bioequivalence study, Auretica is considered bioequivalent with Brilique.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Auretica.

Safety specification

The MAH has submitted the version 0.0 RMP dated 2023-01-30 and proposed the following summary of safety concerns:

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

Assessor's comment: The submitted RMP is in line with the most recent RMP of the originator Brilique and is therefore considered acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The Summary of RMP is considered acceptable.

Conclusion RMP assessment

The MAH has submitted the version 0.0 RMP dated 2023-01-30 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 user test was assessed and accepted at day 70.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Auretica, is found adequate. There are no objections to approval of Auretica, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Auretica, 60 mg, 90 mg, Film-coated tablet was positively finalised on 2024-03-20.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)