LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ticagrelor Newbury
(Ticagrelor)

SE/H/2275/01-02

This module reflects the scientific discussion for the approval of Ticagrelor Newbury. The Public Assessment Report was written in March 2022 by the previous RMS (EE) after initial procedure EE/H/0354/001-002/DC and is attached at the end of this document. RMS transfer from EE to SE was completed 28-04-2022. For information on changes after this date please refer to the module 'Update'.

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Active substance	**ticagrelor**
Pharmaceutical form	**Film-coated tablet**
Strength	**60 mg; 90 mg**
Applicant	**Newbury Pharmaceuticals AB**
EU-Procedure number (origina	**EE/H/0354/01/DC**

Public Assessment Report

Scientific discussion

TICAGRELOR NEWBURY
Ticagrelor

EE/H/0354/001-002/DC

Date: 08.03.2022

This module reflects the scientific discussion for the approval of Ticagrelor Newbury. The procedure was finalised at 19.01.2022. 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 Newbury, film-coated tablet, 60mg and 90mg, from Newbury Pharmaceuticals AB.

The product 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 indications and posology is given in the SmPC.

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

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet intended for oral use contains 60 mg or 90 mg ticagrelor as an active substance.

Excipients included in the formulation of tablet core are mannitol (E421), calcium hydrogen phosphate dihydrate (E341), sodium starch glycolate, hypromellose and magnesium stearate (E470b). Tablet coating includes hypromellose, titanium dioxide (E171), macrogol, iron oxide red (E172) (for 60 mg tablets), iron oxide black (E172) (for 60 mg tablets), iron oxide yellow (E172) (for 90 mg tablets) and talc (E553b) (for 90 mg tablets).

60 mg tablets are round, biconvex, pink tablets debossed with ‘60’ on one side with a diameter of 8 mm. 90 mg tablets are round, biconvex, yellow tablets debossed with ‘90’ on one side with a diameter of 9 mm. Film-coated tablets are packaged to transparent PVC-PVDC/Al blister and inserted to a carton box.

II.2 Drug Substance

INN: Ticagrelor.
Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP).

The Active Substance Master File (ASMF) procedure is used for the active substance. The ASMF has been submitted as an EU ASMF (initial assessment conducted by DE) and AR updated by RMS EE. During the ongoing procedure the monograph of ticagrelor was adopted by Ph. Eur. and included in supplement 10.4. (04/2021:3087). The ASMF was updated accordingly and is considered approvable.

Ticagrelor is a white to or almost white to pale pink powder, practically insoluble in water, freely soluble in methanol, soluble in anhydrous ethanol and practically insoluble in heptane. Ticagrelor contains six chiral centres and herewith exhibits isomerism. The active substance exhibits polymorphism. The polymorphic form has been demonstrated to remain stable. It is not impacted by micronisation.
The manufacturing process has been described in sufficient details, the selected starting materials are in line with principles of ICH Q11.
The active substance specifications, which are in line with the Ph. Eur. monograph for Ticagrelor, are considered adequate to control the quality. Batch analyses data provided from the drug substance manufacturer and from the finished product manufacturer for two batches of ticagrelor, demonstrate compliance with the specifications.

The stability has been tested under ICH conditions. The proposed retest period is 36 months for non-micronized API and 24 months for micronized API, and the recommended storage condition is to preserve in a light-resistant and airtight container, protected by nitrogen gas without applying special temperature storage conditions.

II.3 Medicinal Product

The proposed formulation is an immediate release film-coated tablet containing ticagrelor as an active substance in two strengths 60 mg and 90 mg. The drug product is considered a standard dosage form. In order to differentiate between two strengths, enough measures are taken by the manufacturer by means of colours and debossing of the tablets. The choice of the excipients is justified and their functions explained. All excipients are commonly used for oral pharmaceutical dosage forms.

Ticagrelor is recognized as BCS class IV substance, i.e. low solubility and low permeability. Hence the particle size of drug substance is considered critical with respect to drug dissolution and in vivo performance. Finished product manufacturer has sufficiently demonstrated that polymorphic form of ticagrelor remains unchanged in the drug product.

The chosen manufacturing process is a conventional wet granulation process, described in sufficient details. The drug product manufacturer’s specifications are in line with the Ph. Eur. Monograph for Ticagrelor tablets (07/2021:3097). Analytical procedures have been sufficiently described and the in-house analytical procedures have been fully validated.

Stability studies are carried out in accordance with current ICH/CHMP guidelines. Based on the available stability data, the proposed shelf-life of 36 months without special storage conditions is considered justified.

III. NON-CLINICAL ASPECTS

No new data were presented.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ticagrelor Newbury 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

Pharmacodynamic, pharmacokinetic and toxicological properties of ticagrelor are well known. As ticagrelor is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

A clinical overview on the clinical pharmacology, efficacy and safety has been provided and is considered adequate.

IV.2 Pharmacokinetics

To support the application, the Applicant has submitted as report one bioequivalence study:

- Single dose study no. NCS-596-18-CS, under fasting conditions, 90 mg ticagrelor tablets

Study no. NCS-596-18-CS was an open label, balanced, randomized two-treatment, two-sequence, two-period, single-dose, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions. One tablet containing 90 mg ticagrelor was administered in each period. There was a washout period of 7 days between two treatments.

The primary pharmacokinetic parameters assessed were C_{max} and AUC_{0-t} for ticagrelor. Based on the statistical analysis, test product would be considered bioequivalent to the reference medicinal product if the 90% confidence intervals of the test/reference ratios from the ANOVA of the log transformed data for the pharmacokinetic parameters AUC_{0-t} and C_{max} for ticagrelor fall within the range 80.00% to 125.00%

Study no. NCS-596-18-CS: 90 mg, single dose, fasting conditions

47 subjects were included in the pharmacokinetic and statistical analysis.

Summary of pharmacokinetic parameters for ticagrelor

Treatment	**AUC_{0-t}** ng/ml/h	**C_{max}** ng/ml	****t_{max}** h
Test GM	**6409.353**	**784.724**	3.000
Arithmetic mean ± SD	6652.044 ± 1869.804	810.652 ± 213.062	(1.000 – 5.000)

Reference GM Arithmetic mean ± SD	**6030.920** 6285.110 ± 1823.141	**712.517** 744.812 ± 221.527	2.250 (1.250 – 4.500)
***Ratio** **90% CI**	**106.40** **101.79-111.23**	**110.21** **103.93-116.86**	 n.a.
CV %	12.84	17.03	n.a.

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*
GM geometric mean
**ln-transformed values*
*** median*

Biowaiver

The Applicant has developed two strengths of ticagrelor tablets 90 mg and 60 mg. One bioequivalence study was conducted with the highest strength – 90 mg – under fasting conditions and biowaiver is applied for the additional strength based on a claim that pharmacokinetics of ticagrelor is linear over dose range. According to reference product SmPC, exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.The conduct of only one study with the highest dose is also in line with the recommendations of the EMA product-specific bioequivalence guideline for ticagrelor film-coated tablets (EMA/CHMP/177281/2016/Corr).

The additional 60 mg strength biowaiver was found justified, since the product complied with general biowaiver requirements (i.e. same manufacturer and manufacturing process, same qualitative composition, composition quantitatively proportional). Dissolution similarity for the biowaiver strength was proven in comparisons against bio-batch strength in QC medium and over the physiological pH range without and with surfactant 0.2% Tween 80 included in the dissolution media.

Based on the submitted bioequivalence study, ticagrelor 90 mg film-coated tablets by Labormed-Pharma S.A., Romania, can be considered bioequivalent with the reference product Brilique® by AstraZeneca AB, Sweden. The results of studies 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 Pharmacodynamics

The pharmacodynamic properties of ticagrelor are well known.

IV.4 Clinical efficacy

The efficacy of ticagrelor in the indications approved for the originator Brilique is well established.

IV.5 Clinical safety

The clinical safety of ticagrelor in the indications approved for the originator Brilique is well established.

IV.6 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 Newbury 60 mg and 90 mg film-coated tablet.

- 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

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Increased risk of bleeding	Product information: SPC sections 4.3, 4.4, 4.8, 4.9. PIL sections 2.4.	None
Important Potential Risks		
None	None	None
Missing Information		
Long-term use in patients with prior ischaemic stroke	None	None

Routine pharmacovigilance and routine risk minimisation measures are considered sufficient. The submitted Risk Management Plan is considered acceptable.

IV.7 Discussion on the clinical aspects

Ticagrelor Newbury is intended for generic substitution, consequently, abridged applications avoid the need for repetitive tests on animals and humans.
The reference product is Brilique® (60 mg, 90 mg film-coated tablets) by AstraZeneca AB, Sweden, registered since 03.12.2010. Bioequivalence has been demonstrated between the applicant's product and the reference product Brilique® by AstraZeneca AB, Sweden.
No new or unexpected safety concerns arose from this application.

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 PIL was English.

The results show that the package leaflet 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

The benefit-risk is considered positive and the application for Ticagrelor Newbury 60 mg and 90 mg film-coated tablet has been recommended for approval.

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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)

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