CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Ticagrelor Swyssi 60 mg film-coated tablets
Ticagrelor Swyssi 90 mg film-coated tablets

ticagrelor

SK/H/0295/001-002/DC
Applicant: Swyssi AG, Germany

Date: 12.04.2024

This module reflects the scientific discussion for the approval of Ticagrelor Swyssi 60 mg (90 mg). The procedure was finalised at 11.01.2023.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **Ticagrelor Swyssi 60 mg film-coated tablet and Ticagrelor Swyssi 90 mg film-coated tablet**, from **Swyssi AG, Germany**.

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 sections 4.2 and 5.1).

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."

With Slovakia as the reference member state in this decentralised procedure, the Applicant (Swyssi AG) applied for the marketing authorisation in RMS and CMSs: Austria, Czechia, Greece, Portugal and Romania.
The reference medicinal product is Brilique authorised by AstraZeneca AB ((EU/1/10/655/001-006 and EU/1/10/655/007-011). Brilique has been centrally authorised in the European Union since 03.12.2010.

II. QUALITY ASPECTS

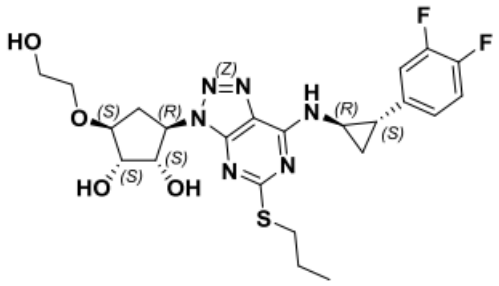
II.1 Introduction

Ticagrelor Swyssi 60 mg film-coated tablets are pink, round, biconvex, film-coated tablets, with a nominal diameter of 8.1 mm, marked with "60" on one side and plain on the other. Each film-coated tablet contains 60 mg ticagrelor.
Excipients used in the drug product (hypromellose 2910, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, titanium dioxide (E171), macrogol 400, talc and iron oxide red (E172)) are well known and widely used as pharmaceutical excipients. Medicinal product is available in packs of transparent PVC/PVDC/Al blisters and/or transparent PVC/PE/PVDC/Al blisters containing 1, 10, 14, 28, 30, 56, 60, 84, 90, 168, 180 film-coated tablets.

Ticagrelor Swyssi 90 mg film-coated tablets are yellow, round, biconvex, film-coated tablets, with a nominal diameter of 9.1 mm, marked with "90" on one side and plain on the other.
Each film-coated tablet contains 90 mg ticagrelor.
Excipients used in the drug product (hypromellose 2910, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, titanium dioxide (E171), macrogol 400, talc and iron oxide yellow (E172)) are well known and widely used as pharmaceutical excipients. Medicinal product is available in packs of transparent PVC/PVDC/Al blisters and/or transparent PVC/PE/PVDC/Al blisters containing 1, 10, 14, 28, 30, 56, 60, 84, 90, 168, 180 film-coated tablets.

II.2 Drug Substance

Ticagrelor structural formula:



Chemical names:
(1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl) -3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

(1S,2S,3R,5S)-3-[7-[[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)- 3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

1,2-Cyclopentanediol, 3-[7-[[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5- (propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-, (1S,2S,3R,5S)-

Appearance: white or almost white to pale pink powder

Solubility: freely soluble in methanol and DMSO, practically insoluble in water

Chirality: there are six chiral carbon atoms in the molecule and ticagrelor is (S,S,R,S,R,S) configuration

Manufacturing: The drug substance ticagrelor is described in the European Pharmacopoeia monograph No. 3087. For the quality documentation of the drug substance, the applicant refers to the Certificate of Suitability from three manufacturers, the information in the certificates has been assessed by EDQM. All three drug substance manufacturers are also responsible for micronisation of the drug substance.

Specifications: The specification for ticagrelor by the drug product manufacturer is generally acceptable and complies with the Ph. Eur. monograph for ticagrelor (04/2021:3087) and with additional tests in line with CEPs (impurities and residual solvents). The specification also includes an additional requirement for particle size distribution and polymorphic identity.

Stability: The re-test period of 36 months and 60 months is presented in the CEPs. Based on 60-month long-term stability data available, re-test period of 60 months was proposed by drug product manufacturer. The satisfactory stability results of micronized batches of ticagrelor have been provided. Based on the results, the stability of the drug substance is not affected by micronization.

II.3 Medicinal Product

Pharmaceutical development: There is Ph. Eur. medicinal product monograph for ticagrelor tablets No. 3097.
The drug product was developed as a generic to Brilique film-coated tablets and it is manufactured in two strengths 60 mg and 90 mg. The development of the product is described in sufficient detail.

Manufacture of the product: The drug product is manufactured by wet granulation and a description of the process has been provided in the dossier. In brief, it involves wet granulation step, drying, mixing, lubrication, tablet compression and coating step. The process validation was conducted on three batches.

Product specification: The proposed specification for the drug product is in line with ICH Q6A, where relevant, and is acceptable.

Stability of the product: Stability data were provided for three batches of each strength under long-term and accelerated conditions which were packed in PVC/PE/PVDC/Al blister and PVC/PVDC/Al blister as proposed for marketing. The proposed shelf-life of 3 years is accepted.

A full nitrosamine risk assessment is presented, no risk of nitrosamines was identified across all potential sources of nitrosamines in the proposed product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented.

III. 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. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ticagrelor Swyssi 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.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence study

To support the application, the Applicant has submitted as report one bioequivalence study conducted under fasting conditions as an open-label, balanced, randomized, single dose, two-treatment, two-period, two-sequence, crossover, oral bioequivalence study to investigate the oral bioequivalence of test product ticagrelor film-coated tablets 90 mg to Brilique (ticagrelor) 90 mg film-coated tablets.

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

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 48)	
	Reference Product (R)	Test Product (T)
C_{max} (ng/mL)	791.235 ± 216.8934 (27.41%)	721.637 ± 187.5243 (25.99%)
T_{max} (hr)#	1.500 (1.00 - 4.50)	2.330 (1.00 - 5.00)
AUC_{0-t} (hr*ng /mL)	6203.388 ± 2128.1814 (34.31%)	6124.115 ± 1741.1980 (28.43%)
$AUC_{0-\infty}$ (hr*ng /mL)	6344.771 ± 2248.8744 (35.44%)	6279.996 ± 1848.9936 (29.44%)
$t_{1/2}$ (hr)	8.368 ± 1.4868 (17.77%)	8.593 ± 1.6927 (19.70%)
λ_z (1/hr)	0.085 ± 0.0152 (17.75%)	0.084 ± 0.0158 (18.96%)
AUC_%Extrap_obs (%)	1.916 ± 1.3596 (70.98%)	2.211 ± 1.5987 (72.32%)

For T_{max} median (min – max).

Table 2. Bioequivalence evaluation of Ticagrelor 18-VIN-0149

PK Parameters (Units)	Geometric Least Squares Means and its ratio (N = 48)			Intra-Subject Coefficient of Variation (%)	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) %			
C_{max} (ng/mL)	698.413	765.252	91.27	14.30	86.92% - 95.83%	100.00
AUC_{0-t} (hr*ng/mL)	5857.760	5892.729	99.41	12.78	95.16% - 103.84%	100.00

Additional data

In vitro dissolution test complementary to bioequivalence study between biobatches of test and reference product has been provided. The dissolution profiles of the test Ticagrelor 90 mg film-coated tablet and reference product Brilique 90 mg film-coated tablet in all dissolution media and QC medium are considered similar in all tested media based on the respective f2 values which are greater than 50.

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study Ticagrelor Swyssi is considered bioequivalent with Brilique.

Biowaiver

A biowaiver was requested for 60 mg formulation of ticagrelor based on bioequivalence study with the 90 mg formulation. Since both strengths (60 mg/90 mg) are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths 60 mg and 90 mg is quantitative proportional, the Applicant provided in vitro dissolution data to confirm the adequacy of waiving additional in vivo bioequivalence testing.

The results of study 18-VIN-0149 with 90 mg formulation can be extrapolated to other strength 60 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.2 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 Swyssi.

- 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 ischemic stroke

IV.3 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application". Bioequivalence between the test product Ticagrelor Swyssi with the reference medicinal product Brilique has been demonstrated based on provided data.

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 Bulgarian.
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

This was the application for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended.
Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovakia acting as the reference member state.

The Applicant (Swyssi AG) has submitted the marketing authorisation under procedural number SK/H/0295/001-002/DC in RMS and CMSs: AT, CZ, EL, PT and RO.

The reference medicinal product is Brilique authorised by AstraZeneca AB. Brilique has been centrally authorised in the European Union since 03.12.2010.

The bioequivalence was demonstrated with the 90 mg strength and all criteria for biowaiver were fulfilled according to BE guideline, therefore, also the biowaiver for strength 60 mg was granted.

Quality aspects of the dossier were adequately described; specifications of ticagrelor were

adequately drawn up and that of finished medicinal product were in line with ICH Q6A.

As ticagrelor is a widely used, well-known active substance, the applicant has not provided additional studies and further non-clinical studies were not required.

Agreement between Member States was reached during the procedure. There was no discussion in the CMDh.

The decentralised procedure was finalised with a positive outcome on 11.01.2023.

No Additional Risk Minimisation Measures have been agreed during the procedure.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.