

Public Assessment Report

Scientific discussion

Eltrombopag STADA Arzneimittel AG 25 mg, 50 mg and 75 mg film-coated tablets

(eltrombopag olamine)

NL/H/5883/001-003/DC

Date: 2 April 2026

This module reflects the scientific discussion for the approval of Eltrombopag STADA Arzneimittel AG 25 mg, 50 mg and 75 mg film-coated tablets. The procedure was finalised on 4 December 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Eltrombopag STADA Arzneimittel AG 25 mg, 50 mg and 75 mg film-coated tablets, from Stada Arzneimittel AG.

The product is indicated:

- for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)
- for the treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)
- In adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.
- [Product name] is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pre-treated and are unsuitable for haematopoietic stem cell transplantation.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

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

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Revolade 25 mg, 50 mg and 75 mg film-coated tablets, which has been registered in the EEA by Novartis Europharm Limited via a centralised procedure (EU/1/10/612) since 11 March 2011.

The concerned member state (CMS) involved in this procedure was Germany.

II. QUALITY ASPECTS

II.1 Introduction

Eltrombopag STADA Arzneimittel AG is a round, biconvex film-coated tablet. The three strengths are distinguishable by their colour, size, and presence (or absence) of a break mark, as follows:

- The 25 mg strength is white to pale yellow, with a diameter of approximately 7 mm and with a breaking notch on one side, dark red to brown at the break. Each tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag. The tablet can be

divided into equal doses.

- The 50 mg strength is brown, with a diameter of approximately 9 mm and with a breaking notch on one side, dark red to brown at the break. Each tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag. The tablet can be divided into equal doses.
- The 75 mg strength is pink, with a diameter of approximately 10 mm. Each tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

The excipients are:

Tablet core - microcrystalline cellulose, mannitol, povidone K90, sodium starch glycolate (type A) and magnesium stearate.

Tablet coating - polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172; only the 50 mg and 75 mg strengths) and iron oxide red (E172; only the 50 mg strength).

The three tablet strengths are dose proportional.

The film-coated tablets are packed in oriented polyamide/aluminium/polyvinyl chloride – aluminium (oPA/Al/PVC-/Al) blisters or perforated unit dose blisters.

II.2 Drug Substance

The drug substance is eltrombopag olamine, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). Eltrombopag olamine is a dark purple crystalline powder, insoluble in water. Eltrombopag olamine exhibits polymorphism. The manufacturing processes followed by two drug substance manufacturers result consistently in the same polymorphic form.

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 in site I follows a convergent reaction strategy with two chemical transformation steps in the first branch and one chemical transformation step in the second branch. Both branches converge in the last chemical transformation of the process, followed by olamine salt formation. No class 1 organic solvents are used. The process in site II comprises three chemical transformation steps in the first branch and two chemical transformation steps in the second branch until eltrombopag olamine is formed. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specifications are considered adequate to control the quality and meet the requirements of the specification of the ASMF-holders, with additional in-house requirements for particle size and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches per site.

Stability of drug substance

For site I, stability data on the drug substance have been provided for several production scale batches (milled and un-milled) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of five years for the unmilled drug substance and three years for the milled drug substance when stored under the stated conditions.

For site II, stability data on the drug substance have been provided for three production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 18 months when stored under the stated conditions.

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 main development studies were the characterisation of the reference products, dissolution method development and performance of formulation optimisation studies. The choice of the QC dissolution method has been justified. The manufacture and composition of the bio-batch used in the bioequivalence study is identical to the marketed product. Comparative dissolution profiles at three pHs have been provided. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of wet granulation, followed by blending, film-coating and packaging and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches of each strength, and two additional small production scale batches of the 75 mg strength, in accordance with the relevant European guidelines. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The tablet core excipients comply with Ph.Eur. requirements. The ready-to-use film-coating materials are controlled according to in-house requirements. 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, average mass, identity, uniformity of dosage units, assay, related substances, microbial limits, nitrosamine impurities and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Appropriate tests for nitrosamine presence are performed on the final product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three pilot scaled batches per strength and two additional smaller scaled batches of the 75 mg 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 two to three production scaled batches per strength stored at 25°C/60% RH (18-24 months) and 40°C/75% RH (6 months). The batches were stored in the intended blisters. The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the provided data, a shelf life was granted of 30 months. No specific storage conditions are needed to be included in the SmPC or on the label.

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 Eltrombopag STADA Arzneimittel AG 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 Eltrombopag STADA Arzneimittel AG is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Revolade which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Eltrombopag olamine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Eltrombopag STADA Arzneimittel AG 75 mg film-coated tablets (Stada Arzneimittel AG, Germany) was compared with the pharmacokinetic profile of the reference product Revolade 75 mg, film-coated tablets (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

A biowaiver for the additional strengths Eltrombopag STADA Arzneimittel AG 25 mg and 50 mg film-coated tablets, referring to the demonstrated bioequivalence study for the 75 mg strength, was requested. The following general requirements for a waiver for additional strength(s), according to the EMA Bioequivalence guideline, are met:

- a. the pharmaceutical products are manufactured by the same manufacturing process,
- b. the qualitative composition of the different strengths is the same,
- c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

- d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The biowaiver can be granted based on the manufacturing procedure, tablet composition and comparative dissolution data provided.

Bioequivalence study

Design Study C1B01303

A single-dose, open label, balanced, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 15 healthy male subjects, aged 21-38 years. Each subject received a single dose (75 mg) of one of the two eltrombopag olamine formulations. The tablet was orally administered with 240 ml water after an overnight fasting of at least 10 hours. There were three dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Dosing under fasting conditions is justified as the immediate release formulation can be taken without food. From the literature it is known that food does not interact with the absorption of eltrombopag olamine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

In total 15 subjects were enrolled, all were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ (median, range)) of eltrombopag olamine, 75 mg under fasted conditions.

Treatment N=15	AUC ₀₋₇₂ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC _{0-∞} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{max} ($\mu\text{g}/\text{mL}$)	t _{max} (h)
Test	98.8 $\pm$ 67.4	117.7 $\pm$ 97.8	7.9 $\pm$ 3.9	3.00 (2.0-5.5)
Reference	94.3 $\pm$ 71.4	109.6 $\pm$ 97.1	8.0 $\pm$ 4.1	3.50 (2.5-4.5)
*Ratio (90% CI)	1.05 (0.97 – 1.13)	107	0.99 (0.92 – 1.07)	--

AUC_{0-∞}	Area under the plasma concentration-time curve from time zero to infinity
AUC₀₋₇₂	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**In-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Eltrombopag STADA Arzneimittel AG is considered bioequivalent with Revolade.

The results of study C1B01303 with 75 mg formulation can be extrapolated to other strengths 25 mg and 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Eltrombopag STADA Arzneimittel AG. At the time of approval, the most recent version of the RMP was version 0.2 dated 18 January 2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	Adult ITP, paediatric ITP, HCV-associated thrombocytopenia and severe aplastic anaemia: • hepatotoxicity • thromboembolic events HCV-associated thrombocytopenia: • hepatic decompensation
Important potential risks	Adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia: • Haematological malignancies • Increased bone marrow reticulin formation Severe aplastic anaemia: • Cytogenetic abnormalities
Missing information	Adult ITP, paediatric ITP, and HCV-associated thrombocytopenia and severe aplastic anaemia: • Patients with hepatic impairment Severe aplastic anaemia: • Use in paediatric population

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 Revolade. 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

The package leaflet (PL) 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.

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 the PL of Revolade, EU number EMEA/H/C/001110, for the content and Ofloxacin STADA 400 mg film-coated tablets, DCP number AT/H/0748, for the lay-out. 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

Eltrombopag STADA Arzneimittel AG 25 mg, 50 mg and 75 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Revolade 25 mg, 50 mg and 75 mg, film-coated tablets. Revolade 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 Eltrombopag STADA Arzneimittel AG with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 December 2024.

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
NL/H/5883/001-003/IA/001	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place	No	22-01-2025	Approved	N.A.
NL/H/5883/001-003/IA/002/G	Change in test procedure for the finished product - Minor changes to an approved test procedure	No	30-05-2025	Approved	N.A.
NL/H/5883/001-003/IA/003/G	Change in test procedure for the finished product - Minor changes to an approved test procedure	No	19-08-2025	Approved	N.A.
NL/H/5883/001-003/IA/004	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Minor changes to an approved test procedure	No	28-10-2025	Approved	N.A.