COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Eltrombopag Devatis 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets

(eltrombopag olamine)

NL/H/5826/001-004/DC

Date: 11 May 2026

This module reflects the scientific discussion for the approval of Eltrombopag Devatis 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets. The procedure was finalised on 29 October 2025. 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 Devatis 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets, from Devatis GmbH.

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
- in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated 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 states (CMS) involved in this procedure were Austria and Germany.

II. QUALITY ASPECTS

II.1 Introduction

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

- The 12.5 mg strength is white to greyish, approximately 6 mm in diameter. Each film-coated tablet contains eltrombopag olamine equivalent to 12.5 mg eltrombopag.
- The 25 mg strength is white, debossed with “25” on one side and approximately 7 mm

in diameter. Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

- The 50 mg strength is brown, debossed with "50" on one side and approximately 9 mm in diameter. Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.
- The 75 mg strength is pink, debossed with "75" on one side and approximately 10 mm in diameter. Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

The excipients are:
Tablet core - microcrystalline cellulose, mannitol, povidon K30, Type A sodium starch glycolate and magnesium stearate (vegetable).
Film-coat – hypromellose, titanium dioxide (E171), macrogol 400, polysorbate 80, iron oxide yellow (E172, only the 50 mg and 75 mg strengths) and iron oxide black (E172, only the 75 mg strength).

The tablet cores of the four strengths are dose proportional.

The film-coated tablets are packed in polyvinyl chloride/polychlorotrifluoroethylene-aluminium (PVC/PCTFE-aluminium) blisters.

II.2 Drug Substance

The active substance is eltrombopag olamine, an established active substance however not described in the European, British or American Pharmacopoeia. The active substance is a brown-dark red crystalline powder and is sparingly soluble in water, very slightly soluble in methanol and N,N-dimethylformamide and soluble in dimethyl sulfoxide. Eltrombopag olamine exhibits polymorphism; form I was consistently produced.

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 comprises two chemical transformation steps with one isolated intermediate, followed by salt formation and micronisation. Adequate specifications have been adopted for starting materials, solvents and reagents. No class 1 solvents are used in the process. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification has been established in-house and is considered adequate to control the quality and to meet the requirements of the specification of the ASMF-holder. Batch analytical data demonstrating compliance with this specification have been provided for six full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for six production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 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 are explained. Particle size has been discussed. The proposed formulation was tested in different studies. The dissolution method is described. The discriminatory capacity of the method has been sufficiently demonstrated. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed. The proposed biowaiver for the lower strengths is acceptable based on the dissolution data of these strengths compared to the dissolution data of the test biobatch at three different pHs.

Manufacturing process
The manufacturing process consists of wet granulation, blending, tablet compression, film-coating and packaging and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four full scaled batches of the common blend, in accordance with the relevant European guidelines. A bracketing approach for the different strengths of the film-coated tablets has been used.

Control of excipients
The excipients comply with Ph.Eur. requirements, or with other relevant compendial requirements. Their 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 description, identification, dissolution, uniformity of dosage units, water content, hardness, assay, related substances and microbial controls. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on four full scaled from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three full scaled batches of the 12.5 mg and 75 mg strength, a bracketing approach is used for the 25 mg and 50 mg strengths. The batches were stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies are performed, demonstrating that the product is photostable. On basis of the data submitted, a shelf life was granted of 3 years for all strengths. No specific storage conditions 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 Devatis 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 Devatis 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 Devatis 75 mg film-coated tablets (Deva Holding A.S., Turkey) 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

The following general requirements were met for waiving the three lower strengths, compared to the 75 mg strength, according to the EMA Bioequivalence guideline:

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 confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence study (AZBE112321)

Design

An open label, balanced, single-dose, randomised, three-period, two-treatment, three-sequence, partial replicate, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 23-44 years. Each subject received a single dose (75 mg) of one of the two eltrombopag formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least eight hours. There were three dosing periods, separated by a washout period of eight days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 34, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Eltrombopag olamine may be taken without reference to food intake. 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, 36 subjects enrolled in the study. One subject was withdrawn due to non-compliance to protocol restrictions during check-in of period III. 35 Subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	**AUC_{0-72} (µg.h/mL)**	**$AUC_{0-\infty}$** (µg.h/mL)	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	184 ± 68	216 ± 92	14.1 ± 4.1	3.50 (2.00 - 4.50)
Reference	184 ± 52	214 ± 66	14.4 ± 3.8	3.50 (1.50 - 5.00)
***Ratio (90% CI)**	0.97 (0.89 – 1.06)	--	0.97 (0.89 - 1.05)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	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

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Eltrombopag Devatis is considered bioequivalent with Revolade 75 mg film-coated tablets.

The results of study AZBE112321 with 75 mg formulation can be extrapolated to other strengths 12.5 mg, 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 Devatis. At the time of approval, the most recent version of the RMP was version 0.2 dated 9 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, HCV-associated thrombocytopenia and severe aplastic anaemia: • Hepatotoxicity • Thromboembolic events HCV-associated thrombocytopenia: • Hepatic decompensation
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.

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 12.5 mg, 25 mg, 50 mg and 75 mg film-coated tablets, EU number EMEA/H/C/001110, for the content and Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules, DCP number NL/H/4989 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 Devatis 12.5 mg, 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 Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 October 2025.

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/5826/001 -004/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	11-2-2026	Approved	N.A.