LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Eltrombopag Viatris Pharma
(eltrombopag, eltrombopag olamine)

SE/H/2663/001-003/DC

This module reflects the scientific discussion for the approval of Eltrombopag Viatris Pharma. The procedure was finalised at 2025-12-22. For information on changes after this date please refer to the module 'Update'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Eltrombopag Viatris Pharma, 25 mg, 50 mg, 75 mg, Film-coated tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX05. TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells. 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). 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 chronic hepatitis C virus (HCV) infection. For the treatment of 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.

II.2 General comments on the submitted dossier

The application for Eltrombopag Viatris Pharma, 25 mg, 50 mg, 75 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CMS as concerned member states (CMS) is the following:
SE/H/2663/001/DC – AT, CZ, DE, DK, EE, ES, FR, HR, IS, IT, LT, NL, NO, PL, PT, SK
SE/H/2663/002/DC – AT, CZ, DE, DK, ES, FR, HR, IS, IT, NL, NO, PL, PT, SK
SE/H/2663/003/DC – AT, DE, DK, ES, FR, HR, IS, IT, NL, NO, PT.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Revolade, 25 mg, film-coated tablet authorised in the Union since 2010, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Revolade, 75 mg, film-coated tablet from Germany with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products
Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Eltrombopag Vale is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to WAYRILZ. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for WAYRILZ in the

treatment of treatment of immune thrombocytopenia, does not prevent the granting of the marketing authorisation of Eltrombopag Vale. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
The Applicant provided inspection outcomes (inspection report and certificate) from inspections performed by competent authorities outside EU from the years around when the study was performed. No issues regarding GCP have been identified.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance 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)
The Applicant has provided an updated ERA report for their eltrombopag product. Revolade (Novartis) was identified as a reference product (RP) with an ERA from 2022. The Applicant has repeatedly asked the originator MAH for a Letter of Access to the studies used in the RP ERA but has obtained permission only to use the ERA summary table accessible in the EPAR and no original studies. Therefore, no new stand-alone ERA could be made for the present product. A PECsw value of 0.75µg/L was calculated for the present product, and this is accepted. According to the current guideline, no new compartments are triggered for eltrombopag, and no new studies are needed. In addition, no increase in environmental exposure is expected with the present product. Therefore, the conclusions of the RP ERA, that eltrombopag does not pose a risk for the environment, are considered valid for the present product. The SmPC section 5.3 of the present product has been harmonized with the RP SmPC.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted a single bioequivalence study comparing Eltrombopag Viatris Pharma with the reference product Revolade.

Pharmacokinetic properties of the active substance

Food interaction:

Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure.

The administration of eltrombopag tablet or powder for oral suspension formulations with a high calcium meal (e.g. a meal that included dairy products) significantly reduced plasma eltrombopag AUC0-∞ and Cmax. In contrast, the administration of eltrombopag 2 hours before or 4 hours after a high calcium meal or with low-calcium food [<50 mg calcium] did not alter plasma eltrombopag exposure to a clinically significant extent.

Administration of a single 50 mg dose of eltrombopag in tablet form with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag mean AUC0-∞ by 59%

and mean Cmax by 65%.

Administration of a single 25 mg dose of eltrombopag as powder for oral suspension with a high calcium, moderate-fat and moderate-calorie meal reduced plasma eltrombopag mean AUC0-∞ by 75% and mean Cmax by 79%. This decrease of exposure was attenuated when a single 25 mg dose of eltrombopag powder for oral suspension was administered 2 hours before a high-calcium meal (mean AUC0-∞ was decreased by 20% and mean Cmax by 14%).

Food low in calcium (<50 mg calcium), including fruit, lean ham, beef and unfortified (no added calcium, magnesium or iron) fruit juice, unfortified soya milk and unfortified grain, did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content.

Linearity:

No accumulation of plasma eltrombopag AUC(0-τ) was observed after QD dosing at 5 mg and 10 mg; however, 37-56% accumulation was observed after QD dosing of 20 mg, 30 mg, 50 mg, and 75 mg for 10 days. Single dose plasma eltrombopag AUC(0-∞) and Cmax values increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90%) CI) 1.13 (1.04, 1.22) for AUC(0-∞) and 1.15 (1.07, 1.24) for Cmax over a range of 5 mg to 75 mg. Steady-state plasma eltrombopag AUC(0-τ) and Cmax increased with increasing dose in a slightly greater than dose proportional manner where the slope estimate (90% CI) was 1.19 (1.11, 1.26) for AUC(0-τ) and 1.20 (1.12, 1.27) for Cmax over a range of 5 mg to 75 mg QD.

Elimination:

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20% of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Study C23137

Methods

This was a two-treatment, four-period, two-sequence, full replicate, single-dose crossover study conducted in 44 healthy volunteers, comparing Eltrombopag Viatris Pharma, 75 mg, film-coated tablet with Revolade, 75 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 120 hours post-dose. Plasma concentrations of Eltrombopag were determined with an 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 06/03/2024 and 17/05/2024.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Eltrombopag, n=43.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	200581.38 ± 65151.08	10020.72 ± 2877.60	4.000 (2.000 - 8.000)
Reference	218509.94 ± 74205.15	11240.02 ± 2934.24	3.500 (1.500 - 8.000)
***Ratio (90% CI)**	92.77 (88.12 - 97.66)	89.45 (84.31 - 94.91)	-

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%.

Pre-dose concentrations were detected in 30 of the subjects (test product) and 30 of the subjects (reference product). Given that none of the predose concentrations was higher than 5% of the Cmax of each subject, this is not likely to affect the outcome of the study.

A biowaiver was sought for the additional strengths of 25 and 50 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). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 25 and 50 mg is acceptable, as all conditions for biowaiver for additional strength, 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 eltrombopag is slightly greater then dose proportional between 25 mg and 75 mg but within the linearity criteria ±25% according to the bioequivalence guideline.

Based on the submitted bioequivalence study, Eltrombopag Viatris Pharma is considered bioequivalent with Revolade.

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.

Pharmacovigilance system
RMS, AT, CZ, DK, EE, HR, IS, LT, NO, PL, PT, SK Proposed MAH: [Viatris Limited]

DE Proposed MAH: Mylan Germany GmbH

IT Proposed MAH: Mylan S.p.A. Con Socio Unico

NL Proposed MAH: Mylan Pharmaceuticals Limited

FR Proposed MAH: Viatris Santé

ES, Proposed MAH: Viatris Pharmaceuticals S.L.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Viatris Pharma.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2025-01-07 for Eltrombopag Viatris Pharma.

Summary of Safety Concerns	
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** • Increased Bone Marrow Reticulin Formation • Haematological malignancies **Severe aplastic anaemia** • Cytogenetic abnormalities
Missing Information	**Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia** • Patients with hepatic impairment **Severe aplastic anaemia** • Use in paediatric population

Part III Pharmacovigilance Plan

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2025-01-07 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

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Common renewal date

- The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Eltrombopag Viatris Pharma, is found adequate. There are no objections to approval of Eltrombopag Viatris Pharma, 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.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Revolade (content) and Dimethyl fumarate Taw (layout).

The bridging was assessed and accepted at day 70.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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