LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Eltrombopag Teva
(eltrombopag olamine)

SE/H/2405/01-03/DC

This module reflects the scientific discussion for the approval of Eltrombopag Teva. The procedure was finalised on 2024-12-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Eltrombopag Teva, 25 mg, 50 mg, 75 mg, Film-coated tablet.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Eltrombopag Teva, 25 mg, 50 mg, 75 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS):
SE/H/2405/01/DC: AT, BG, CY, CZ, DE, DK, EE, EL, ES, FR, HR, IE, IT, LT, LV, NL, NO, PT, RO, SI, SK
SE/H/2405/02/DC: AT, CY, CZ, DE, DK, EL, ES, FR, HR, IE, IT, NL, NO, PT, RO, SI, SK
SE/H/2405/03/DC: AT, CZ, DE, DK, ES, FR, IT, NL, NO, PT, RO, SK

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 European Union since 2010, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Revolade, 25 mg and 75 mg, film-coated tablet from Germany with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of eltrombopag are well known. As eltrombopag is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Eltrombopag Teva is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Eltrombopag Teva from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 2 bioequivalence studies comparing Eltrombopag Teva with the reference product Revolade.

Pharmacokinetic properties of the active substance

Absorption:
Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%. The tablets should be taken at least two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc).

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 BE-2175-21 (25 MG)

Methods
This was a single-dose, three-way crossover study conducted in 78 healthy volunteers (64 completed all study periods), comparing Eltrombopag Teva, 25 mg, film-coated tablets with Revolade, 25 mg, film-coated tablets under fasting conditions. The study also included a Canadian reference product. Blood samples for concentration analysis were collected pre-dose and up to 72 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 27 March 2023 and 28 April 2023.

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.

Eltrombopag study# BE-2175-21 (Statistical results for subjects receiving test and EU Reference product, N=65)						
Parameter	Test GeoLSM	RefGeo LSM	Ratio%	90% C. I.	Power (%)	BE
LnC_{max}	4039.26	3874.35	104.26	98.14 - 110.75	100	Yes
$LnAUC_{0-t}$	49314.63	48986.04	100.67	95.42 - 106.21	100	Yes

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%.

Study BE-2152-21 (75 MG)

Methods
This was a single-dose, two-way crossover study conducted in 80 healthy volunteers (72 completed the study), comparing Eltrombopag Teva, 75 mg, film-coated tablets with Revolade, 75 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 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 20 April 2023 and 08 May 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for eltrombopag, n=72.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**136538.84 ± 43404.227**	**11497.48 ± 3545.196**	**3.00 (1.50-5.00)**
Reference	**128067.33 ± 44797.004**	**10473.35 ± 3516.538**	**3.50 (1.50-6.00)**
***Ratio (90% CI)**	**105.96 [97.65-114.97]**	**109.77 [100.35-120.08]**	**-**
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%.

A biowaiver was sought for the additional strength of 50 mg.

Discussion and overall conclusion
The bioequivalence studies and their 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). In studies with more than two treatment arms (e.g. a three period study including two references, one from EU market and another from non-EU market), the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question. Therefore, the treatment arm concerning the Canadian reference product will be disregarded and not assessed (study BE-2175-21). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, from a pharmacokinetic perspective, Eltrombopag Teva is considered bioequivalent with Revolade.

The results of studies BE-2175-21 and BE-2152-21 with 25 and 75 mg formulations, respectively, CAN be extrapolated to other strength 50 mg, according to conditions in the Guideline on the investigation of bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6., “Bracketing approach”.

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.

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 Teva.

Part II Safety specification
The MAH has submitted the version 1.0 RMP dated 2023-08-17 and proposed the following summary safety concerns:

List of important risks and missing information	
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 1.0 signed 2023-08-17 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.

V. USER CONSULTATION

The user test was assessed and accepted at day 70.

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 PlL 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 quality of the generic product, Eltrombopag Teva, is found adequate. There are no objections to approval of Eltrombopag Teva, 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.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Eltrombopag Teva, 25 mg, 50 mg, 75 mg, film-coated tablet was positively finalised on 2024-12-04.

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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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