COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Relatrom 25 mg and 50 mg, film-coated tablets

(eltrombopag olamine)

NL/H/5703/001-002/DC

Date: 20 September 2024

This module reflects the scientific discussion for the approval of Relatrom 25 mg and 50 mg, film-coated tablets. The procedure was finalised on 8 January 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 Relatrom 25 mg and 50 mg, film-coated tablets, from Rafarm SA.

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) (see SmPC sections 4.2 and 5.1).
- 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) (see SmPC sections 4.2 and 5.1).
- 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 (see SmPC sections 4.4 and 5.1).
- 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 (see SmPC section 5.1).

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 12.5 mg, 25 mg, 50 mg and 75 mg, film-coated tablets, which has been registered by Novartis Europharm Limited since 11 March 2010 in the EEA via a centralised procedure (EU/1/10/612).

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

II. QUALITY ASPECTS

II.1 Introduction

Relatrom is a round, biconvex film-coated tablet:

- The 25 mg strength is dark pink and debossed with “II” on one side. Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.
- The 50 mg strength is pink and debossed with “III” on one side. Each film-coated tablet

contains eltrombopag olamine equivalent to 50 mg eltrombopag.

The excipients are:
Tablet core - microcrystalline cellulose, mannitol, povidone, isomalt (E953), calcium silicate, sodium starch glycolate and magnesium stearate
Tablet coating – hypromellose, titanium dioxide (E171), red iron oxide (E172), triacetin and yellow iron oxide (E172).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in oPA/Al/PVC-Al blisters.

II.2 Drug Substance

The active substance is eltrombopag olamine, an established active substance however not described in the European or British Pharmacopoeia. Eltrombopag olamine is a red to brown crystalline powder and is sparingly soluble in dimethyl sulfoxide and insoluble in methanol. Furthermore, eltrombopag olamine is insoluble in aqueous buffers in the physiological range (below 0.02 mg/ml). Eltrombopag olamine exhibits polymorphism; however, the manufacturing processes followed by the drug substance manufacturer consistently result in Form I. No conversion of the polymorphic form during the manufacturing process and stability studies was observed.

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 follows a convergent reaction strategy with four chemical transformations in the first branch and two chemical transformations in the second. Both branches converge in the last chemical transformation of the process, followed by the olamine salt formation. 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 specification is considered adequate to control the quality and meets the requirements of the specification of the ASMF-holder. All in-house methods for drug substance control are adequately described and validated in the dossier. Batch analytical data demonstrating compliance with the proposed drug substance specification has been provided by the drug product manufacturer for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for stored at 25°C/60% RH (up to 72 months) and 40°C/75% RH (6 months). 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. The manufacture and composition of the bio-batch used in the bioequivalence studies is identical to the marketed product. Comparative dissolution profiles at three pHs have been provided. Due to the poor aqueous solubility of the drug substance, comparative dissolution with the addition of a surfactant is also provided. The pharmaceutical development of the product has generally been adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation, followed by compression and film-coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three small production scale batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. The process validation protocol for large product scale batch size is provided.

Control of excipients
The excipients comply with Ph. Eur. requirements were applicable, or with other relevant compendial 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 description, identification, dissolution, assay, related substances and uniformity of dosage units. The absence of a test for microbial quality was adequately justified. 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 from three commercial sized batches per 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 three production scaled batches per strength stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended blisters. The drug product is generally very stable in the proposed container packaging system and no general trends or signs of degradation are observable. Photostability data in accordance with ICH show that the product is stable when exposed to

light. Based on the provided data, the proposed shelf-life of 24 months with no special storage condition is acceptable.

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 Relatrom 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 Relatrom 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 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Relatrom 75 mg, film-coated tablets (Rafarm SA, Greece) 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 strengths Relatrom 25 mg and 50 mg film-coated tablets, referring to the demonstrated bioequivalence study for the 75 mg strength, is accepted. The following general requirements in line with 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 is 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

A single-dose, open label, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 62 healthy male and female subjects, aged 20-44 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 fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 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
One subject had an adverse event (vomiting) and one subject withdrew consent and were withdrawn from the study. Therefore, a total of 60 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=60	**AUC_{0-72}** (µg.h/mL)	**C_{max}** (µg/mL)	**t_{max}** (h)
Test	151.30 ± 47.46	14.43 ± 3.41	3.00 (1.50-5.50)
Reference	152.80 ± 50.54	14.18 ± 3.61	3.50 (2.00-6.00)
***Ratio (90% CI)**	1.00 (0.94-1.06)	1.02 (0.96-1.08)	--

AUC_{0-72} 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

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Relatrom is considered bioequivalent with Revolade.

The results of the study 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 Relatrom.

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. No new clinical studies were conducted. 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

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 for content and Clozapine 12.5 mg oro-dispersible tablets for 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

Relatrom 25 mg and 50 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Revolade 25 mg and 50 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 Relatrom with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 January 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/5703/1-2/IB/001	A.2.b. Change in the (invented) name of the medicinal product for Nationally Authorised Products	Yes	25-04-2024	Approved	NA
NL/H/5703/IB/002/G	- B.I.a.1.a: Addition of a manufacturer for a starting material - B.I.a.3.a: Up to 10-fold increase in batch size in the manufacturing process of the active substance - B.I.b.1.b: Tightening of specification limits - B.I.b.2.a: Minor changes to an approved test procedure	No	22-05-2024	Approved	NA