17 October 2024
EMA/510859/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eltrombopag Viatris

International non-proprietary name: eltrombopag

Procedure No. EMEA/H/C/006417/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ASMF	Active substance master file = drug master file
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CMS	Concerned Member State
CoA	Certificate of analysis
CQA	Critical quality attribute
CRS	Chemical reference substance
DL	Detection limit
DMF	Drug master file = active substance master file, ASMF
DSC	Differential scanning calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
EU	European Union
FID	Flame ionisation detection
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
HPLC	High performance liquid chromatography
HS-GC	Headspace-gas chromatography
ICH	International conference on harmonisation
IR	Infra-red
KF	Karl Fischer titration
LoA	Letter of access
LOD	Loss on drying
LoD	Limit of detection
LoQ	Limit of quantitation
MAH	Marketing authorisation holder
MS	Mass spectroscopy
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PDA	Photo diode array
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QL	Quantitation limit
QOS	Quality overall summary
QTTP	Quality target product profile
RH	Relative humidity
RMS	Reference member state
RSD	Relative standard deviation
Rrt	Relative retention time
Rt	Retention time
Rt	Room temperature
SD	Standard deviation
SWFI	Sterile water for injections
TGA	Thermo-gravimetric analysis
TLC	Thin layer chromatography
UV	Ultra violet
XRD	X-Ray diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 27 November 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Eltrombopag Viatris, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Eltrombopag Viatris is indicated for the treatment of

- adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

- 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 sections 4.2 and 5.1).

- 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 sections 4.4 and 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Revolade instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Revolade, 12.5 mg, 25 mg, 50 mg, 75 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 2010-03-11
- Marketing authorisation granted by:

  - Union
- Marketing authorisation numbers:

  12.5 mg - EU/1/10/612/010-012

  25 mg - EU/1/10/612/001-003

  50 mg - EU/1/10/612/004-006

  75 mg - EU/1/10/612/007-009

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Revolade, 12.5 mg, 25 mg, 50 mg, 75 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: (dd-mm-yyyy) 2010-03-11
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers:

  12.5 mg - EU/1/10/612/010-012

  25 mg - EU/1/10/612/001-003

  50 mg - EU/1/10/612/004-006

  75 mg - EU/1/10/612/007-009

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Revolade 75 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 2010-03-11
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/10/612/007-009
- Bioavailability study number(s): C1B00915

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Hjalti Kristinsson

The Rapporteur appointed by the PRAC was:

Rapporteur: Monica Martinez Redondo

The application was received by the EMA on	27 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	18 March 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	03 April 2023
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP consolidated list of outstanding issues on	24 September 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	01 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Eltrombopag Viatris on	17/10/2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC as amended.

The applicant has developed Eltrombopag Viatris 12.5 mg, 25 mg, 50 mg and 75 mg Film-coated tablet as generic to the reference product Revolade 12.5 mg, 25 mg, 50 mg and 75 mg Film-coated tablet.

The indication as presented in the proposed SmPC is shown below.

- Eltrombopag Viatris is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).
- Eltrombopag Viatris is indicated 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 sections 4.2 and 5.1).
- Eltrombopag Viatris is indicated 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 sections 4.4 and 5.1).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 12.5 mg, 25 mg, 50 mg and 75 mg of eltrombopag (as eltrombopag olamine) as active substance.

Other ingredients are:

Tablet core: magnesium stearate, mannitol (E421), microcrystalline cellulose (E463), povidone, sodium starch glycolate, and hydroxypropylcellulose.

Tablet coating: hypromellose (E464), macrogol 3350 (E1521), titanium dioxide (E171), talc (E553b), iron oxide red (E172ii) (50 mg and 75 mg strengths), iron oxide yellow (E172iii) (50 mg strength), and indigo carmine (E132) (50 mg and 75 mg strengths).

The product is available in aluminium blisters (OPA/Alu/PVC/Alu) as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is 3’-{(2Z)-2-[1-(3,4-dimethylphenyl)-3-methyl-5-oxo-l,5 dihydro-4H-pyrazol-4ylidene]hydrazine}-2'-hydroxy-3-biphenyl carboxylic acid-2-aminoethanol

corresponding to the molecular formula $C_{25}H_{22}N_4O_4.C_4H_{14}N_2O_2$. It has a relative molecular mass of 564.27 g/mol and the following structure:

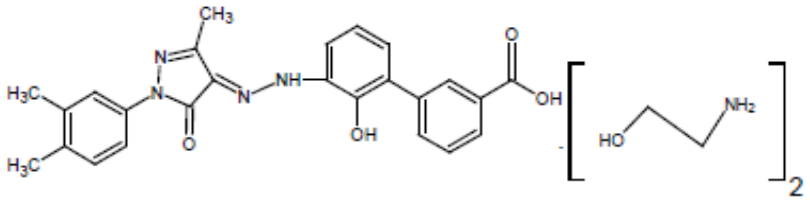

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of infrared spectroscopy (IR), ultra-violet (UV) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy (^1H, ^{13}C, HSQC NMR - ^1H -^{13}C, HMBC NMR - ^1H -^{13}C, ID-NOE - ^1H -^1H), mass spectrometry and elemental analysis. The solid state properties of the active substance were measured by XRD.

The active substance is a non-hygroscopic brown to red crystalline powder very slightly soluble in methanol and dimethylformamide. It is insoluble in water and aqueous media (pH 1.2, 4.5, and 6.8).

The active substance has a non - chiral molecular structure but is in the Z configuration.

Eltrombopag olamine exhibits polymorphism; however, the manufacturing processes followed consistently results in Form I.

Manufacture, characterisation and process controls

Two sources of the active substance are used. Satisfactory GMP documentation has been provided for both sites.

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF by both manufacturers and it was considered satisfactory.

Both ASMFs have undergone workshare procedure and both were approved in 2023.

Eltrombopag is synthesized in a branched synthetic scheme consisting of 5-7 main synthetic steps and a final purification. Two starting materials are declared (in both ASMFs), they are commercially available, well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Potential impurities arising from the manufacturing process have been evaluated and necessary controls have been incorporated to reflect compliance with the ICH Q3A, ICH Q3C, ICH Q3D and ICH M7 recommendations.

The active substance is packaged in transparent bag, and the bag is tied with a plastic tag which complies with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification tested by the finished product manufacturer includes tests for appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC, XRD), loss on drying (Ph. Eur.), water content (Ph. Eur.), residue on ignition/sulphated ash (Ph. Eur.), olamine content / ethanolamine content (Ph. Eur.), related substances (HPLC), assay (HPLC), acetic acid content (Ph. Eur., HPLC), palladium content (Ph. Eur., In house), hydrazine content (Ph. Eur., GC-MS), ethylene oxide content (Ph. Eur., GC), determination of NDMA, NDEA, NIPEA and NDIPA (Ph. Eur., LC-MS), residual solvents (Ph. Eur., HS-GC), and particle size distribution (Ph. Eur. and in house)

All impurities are limited with respect to applicable guideline (ICH Q3A, Q3C and Q3D).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analyses data of the active substance (three production scale batches from each site) are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, loss on drying, water content, related substances, and assay.

The results of six months accelerated and sixty months' long-term stability data show that there is no significant change in any of the parameters studied.

Results on stress conditions at solid state (ambient temperature (25± 2°C for a week), thermal (105°C for a week), humidity (90% RH for a week), exposure to light and at liquid state (hydrolysis), acid hydrolysis (HCl), base hydrolysis (NaOH), oxidation (H_20_2) were also provided on one batch. The results obtained in this study demonstrate, that the methods used for the determination of related compounds are stability indicating. Therefore the methods are suitable for their intended use.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 60 months in well closed containers and store at controlled room temperature i.e. between 20ºC and 25ºC (excursions are allowed between 15ºC and 30ºC) in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as:

12.5 mg strength: white, round, biconvex, film-coated tablet (approximately 6 mm in diameter) debossed with 'L' on one side.

25 mg strength: white, round, biconvex, film-coated tablet (approximately 7 mm in diameter) debossed with '25' on one side.

50 mg strength: brown, round, biconvex, film-coated tablet (approximately 10 mm in diameter) debossed with '50' on one side.

75 mg film-coated: pink, round, biconvex, film-coated tablet (approximately 11 mm in diameter) debossed with '75' on one side.

The finished product has been developed to be a generic equivalent to the reference medicinal product Revolade. Consequently, the objective was to prepare film-coated tablets being essentially similar to the reference medicinal product.

The key characteristics of the active substance that have been taken into consideration during pharmaceutical development of the finished products are as follows: solubility, pH, partition coefficient, Log P, dissociation constant [pKa], melting range, isomerism, solid state form, hygroscopicity, stability, and pharmacokinetic properties. The aforementioned summary of the active substance characteristics was used to set up a preliminary risk assessment addressing the potential risks of the active substance for the finished product critical quality attributes (CQAs).

Compatibility of the active substance and excipients has been demonstrated with binary samples under stability.

The same excipients are employed for the applied product and the reference product, with the exception of hydroxypropyl cellulose low substituted used only in the applied product. Additionally, regarding coating, talc is used in the applied product and polysorbate 80 for the reference product while iron oxide black is used in the reference product and indigo carmine in the applied product.

The selected excipients are all common and known pharmacopoeial excipients, and controlled according to relevant Ph. Eur. monograph, with the exception of iron oxide and indigo carmine, which is controlled in line with EU regulation 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The particle size of the low soluble active substance was also studied as it is a factor that may affect active substance release and process robustness. In addition, the physical and chemical stability of the selected active substance was evaluated, in order to assure product consistency over shelf-life.

The results and outcomes of the developmental efforts were also assured with extensive testing through out the development, scale up and the production of scale up and exhibit batches. The overall effort was validated through the clinical trials.

During evaluation, the quality target product profile (QTPP) was defined based on the properties of the active substance, clinical and pharmacokinetic (PK), characteristics, of the reference products, characterization of the RMP (reference medicinal product)product, as well as on consideration of the RMP label and intended patient population.

A solubility study was conducted in order to evaluate the solubility of eltrombopag, in buffers covering a pH range between 1.2 and 6.8.

The conditions for the in vitro dissolution method were selected based on the recommendations set in the Guideline on the Investigation of Bioequivalence.

Comparative dissolution results between generic and reference medicinal product biobatches were presented for the 75 mg product strength.

A biowaiver request for the tablets of the lower strengths (i.e. 12.5, 25 and 50 mg) has been supported by dissolution profile comparisons between the 75 mg film-coated tablets generic biobatch and the lower strengths according to the Guideline on the investigation of bioequivalence (Rev.1). The

calculated *f2* values of the dissolution profiles comparison could support the biowaiver request from a chemical-pharmaceutical point of view for the 12.5, 25 and 50 mg product strengths.

The discriminatory power of the selected dissolution method against changes in composition and manufacturing process has been demonstrated.

In relation to the manufacturing process development wet granulation was pursued and chosen to manufacture the commercial finished product.. For each process step, a risk assessment was conducted to identify potentially high risk process factors which could impact the identified intermediate and the finished product CQAs. These variables were then investigated in order to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch.

The primary packaging is aluminium blisters (OPA/Alu/PVC/Alu). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site. Satisfactory GMP documentation has been provided.

The manufacturing process consists of 14 main steps: mixing, wet granulation, drying, lubrication, tabletting (compression), coating, and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications shown include appropriate tests for this kind of dosage form: appearance (visual), average weight (weighting), disintegration (Ph. Eur.), uniformity of dosage units (Ph. Eur.), identification (HPLC, UV), identification of colorants (In-House), water content (KF), dissolution (Ph. Eur.), assay (HPLC), related substances (HPLC), and microbiological test (Ph. Eur.).

The specifications for related substances have been set according to ICH Q 3 B (R2) Impurities in New Drug Products (CPMP/ICH/2738/99).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. Regarding manufacturing equipment, it is stated that there is no more than a low contribution to the elemental impurity content during manufacturing process from equipment. This refers also to primary packaging materials. Water quality used in manufacturing process is also monitored periodically concerning elemental impurities levels. Regarding active substances and excipients, data indicating cumulative expected maximum elemental impurity intake in the tablets is provided. It can be seen that all class 1, class 2a and class 2b elemental impurities are likely to be present at levels below 30% of specification level as per ICH. Palladium used by both active

manufacturers as catalyst has been taken into account. Based on these data, it is concluded that no further control of these elemental impurities is required.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches per strength of finished product stored for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, average weight, water content, disintegration, dissolution, assay, related substances, and microbiological tests The analytical procedures used are stability indicating.

No significant changes have been observed at any of the tested conditions under long term and accelerated conditions.

A degradation study was performed. Samples of 1 batch of the 12.5 mg strength (as it is considered the worst case scenario) were exposed to heat, acidic hydrolysis, basic hydrolysis, peroxide oxidation and light according to ICH guideline Q1B. The finished product degrades significantly under oxidative, acidic and basic hydrolytic conditions. Heating has no significant impact on the product, showing that the molecule is very stable even under extreme exposure (20 days at 80 ºC). The final product is proven stable when exposed to photoirradiation, according to ICH guideline Q1B, even without any packaging material. It was concluded that the methods used for assay and related substances have presented satisfactory mass balance and are considered stability indicating.

Based on available stability data, the proposed shelf-life of 48 months without storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Eltrombopag Viatris manufactured by Viatris Limited is considered unlikely to result in any significant increase in the combined sales volumes for all eltrombopag containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the proposed SmPC are identical to the reference product Revolade.

The submitted non-clinical overview on the pre-clinical pharmacology, pharmacokinetics, and toxicology of Eltrombopag is adequate. Grounds for non-providing new clinical data are adequately justified. The impurity profile and the safety of the excipients are considered acceptable.

Since Eltrombopag Viatris is a generic product which does not include the addition of a new indication, a new patient population, or an increase in the maximum recommended therapeutic dose, it will not

lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

2.3.4. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film coating tablets containing 12.5 mg, 25 mg, 50 mg and 75 mg of eltrombopag. To support the marketing authorisation application, the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for this application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A strength based biowaiver is applied for the additional strengths of 12.5 mg, 25 mg and 50 mg based on the in vivo data (bioequivalence study) of the 75 mg strength. The applicant has provided a justification supporting the linearity and furthermore done bootstrap analysis for the biowaiver of additional strengths (12.5 mg and 25 mg) at pH 6.8 with the software of Bootf2bca. The output was provided, and the bootstrap parameters are acceptable as for all strengths the lower 90% confidence interval was 50 or more, thus demonstrating similar in vitro release at pH 6.8. The biowaiver is acceptable in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr **).

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Study title
An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of Eltrombopag olamine 75 mg film-coated tablets of test product and Revolade 75 mg filmtabletten (film-coated tablets) of Novartis Europharm Limited., Ireland in healthy, adult, human subjects under fasting conditions.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

An open label, balanced, randomized, single-dose, two-treatment two-sequence, two-period, crossover bioequivalence study of Eltrombopag olamine 75 mg film-coated tablets of Elpen Pharmaceutical Co Inc., Greece and Revolade 75 mg filmtabletten (film-coated tablets) of Novartis Europharm Limited., Ireland in healthy, adult, human subjects under fasting conditions.

Methods

- **Study design**

The study was an open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two 75 mg eltrombopag film-coated tablet formulations in 56 healthy subjects under fasting conditions.

- **Test and reference products**

Eltrombopag Viatris 75 mg has been compared to Revolade (Eltrombopag) 75 mg film-coated tablets - MAH: Novartis Europharm Limited, Ireland.

Treatment	
Test Product	Eltrombopag film-coated tablets, 75 mg Manufactured by: Elpen Pharmaceuticals Co. Inc., Greece
Reference Product	Revolade (Eltrombopag) 75 mg film-coated tablets MAH: Novartis Europharm Limited, Ireland. Lot: BTP28 EXP 2/2023

- **Population(s) studied**

Fifty-six (56 + 03 standby) healthy adult subjects were admitted to the study (00 females and 56 males; 19-44 years, BMI 18.6-29.8 kg/m^2) and dosed in period 1. Fifty-four (54) subjects were dosed in period 2 (subjects 19 and 49 withdraw their consent). Total of fifty-three (53) subjects completed the study and were included in the pharmacokinetic and statistical analysis (excluding subjects no. 06, 19 and 49).

The study population was chosen according to the Guideline on the Investigation of Bioequivalence.

Protocol deviations

No major protocol deviations were reported.

- **Analytical methods**

The study samples were analysed by an LC method with MS/MS detection after hybrid (protein precipitation + solid phase) extraction using eltrombopag-13C4 as internal standard for the detection of eltrombopag olamine.

The method validation report for the determination of eltrombopag olamine has been provided. The method was fully and partially validated in human plasma.

Bioanalytical method validation was evaluated according to the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)

- **Pharmacokinetic variables**

The primary pharmacokinetic parameters for this study were AUC_{0-72} and C_{max} and the secondary pharmacokinetic parameters was T_{max}.

- **Statistical methods**

The Ln-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) were statistically analysed using PROC GLM from SAS for difference due to treatment, period, sequence and subject (sequence) as a fixed effect. Treatment and period effects were tested using mean square error and sequence effect was tested using subject (sequence) as the error term at 5% level of significance.

Results

Table 1: Pharmacokinetic parameters for eltrombopag (non-transformed values)

Pharmacokinetic parameter	**Test (N=53)**	**Reference (N=53)**
	arithmetic mean ± SD	**arithmetic mean ± SD**
$AUC_{(0-72h)}$ (µg/mL) *(hr)	96.976±37.856	107.087±41.368
C_{max} (µg/mL)	7.894±2.806	8.943±3.111
T_{max}*	4.000 (2.000-6.000)	3.333 (1.500-6.000)

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Table 2: Statistical analysis for eltrombopag (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%**
$AUC_{(0-72)}$ (h*µg/mL)	90.91	84.95 – 97.29%	21.071
C_{max} (µg/mL)	88.43	82.19 – 95.15%	22.796

Results of the study confirm that the test product is bioequivalent with the EU reference product under fasting conditions as the 90% CI of the ratio for geometric least square means of log-transformed data

of AUC_{0-72} and C_{max} for eltrombopag of the test product and reference product fell within the conventional acceptance criterion of 80.00-125.00%.

- **Safety data**

A total of four (04) adverse events were reported by four (04) subjects during the study. All AEs were mild in severity. There were four (04) AEs (conjunctivitis, blood creatinine increased, alanine aminotransferase increased and blood bilirubin increased) which were considered unlikely related to the reference product. There were no serious adverse events during the conduct of this study.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety of eltrombopag is adequate. A bioequivalence study was conducted with the highest strength (75 mg) and biowaiver requested for the lower strengths (12.5 mg, 25 mg, and 50 mg) of the test product.

To support this application, the applicant submitted one bioequivalence study. The study was a, open label, single dose, randomized, 2-period, 2-sequence, cross-over bioequivalence study of two products of eltrombopag film-coated tablet 75 mg in healthy, adult human subjects under fasting conditions. A total of 56 subjects were enrolled and dosed in period 1, in line with the protocol. Fifty-three (53) subjects were included in the PK and statistical analysis.

The pivotal bioequivalence study was conducted in line with the general bioequivalence guidance in terms of design, analyte and parameters for bioequivalence assessment.

The test product was compared to the EU reference product under fasting conditions in line with current guidance.

The results of study indicate that the test product was bioequivalent with the EU reference product under fasting conditions as the 90% CI of the ratio for geometric least square means of log-transformed data of AUC_{0-t} and C_{max} for eltrombopag of the test product and reference product fell within the conventional acceptance criterion of 80.00-125.00%.

The results of the bioequivalence study can be extrapolated to the additional strengths according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr*, section 4.1.6).

2.4.4. Conclusions on clinical aspects

Eltrombopag Viatris film-coated tablets, 75 mg, is bioequivalent with Revolade 75 mg film-coated tablets based on the presented study under fasting conditions.

The results of study with 75 mg formulation can be extrapolated to other strengths (50 mg, 25 mg and 12.5 mg) according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr*, section 4.1.6.

Approval is recommended from the clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 3: Summary of safety concerns

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

* Severe aplastic anaemia is not currently included as an indication for Eltrombopag Viatris.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Hepatotoxicity	<u>Routine risk minimisation measures:</u> SmPC section 4.2, 4.4 and 4.8. PL section 4. <u>Additional risk minimisation measures</u> None	Routine pharmacovigilance activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thromboembolic events	Routine risk communication: SmPC section 4.2, 4.4, 4.8 and 4.9 PL section 2 and 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
HCV-associated thrombocytopenia Hepatic decompensation	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.8. PL section 2 and 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia* Increased Bone Marrow Reticulin Formation	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Haematological malignancies	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Severe aplastic anaemia* Cytogenetic abnormalities	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 4. Additional risk minimisation measures None	Routine pharmacovigilance activities
Adult ITP, Paediatric ITP, HCV-associated thrombocytopenia, and severe aplastic anaemia*	Routine risk minimisation measures: SmPC section 4.2 PL section 2.	Routine pharmacovigilance activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients with hepatic impairment	Additional risk minimisation measures None	
Severe aplastic anaemia* Use in paediatric population	Routine risk minimisation measures: SmPC section 4.2 PL section 2 Additional risk minimisation measures None	Routine pharmacovigilance activities

* Severe aplastic anaemia is not currently included as an indication for Eltrombopag Viatris

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic safety update reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Revolade and another Mylan/Viatris product. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of eltrombopag film-coated tablets. The reference product Revolade is indicated for the treatment of:

- adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

- 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 sections 4.2 and 5.1).

- 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 sections 4.4 and 5.1).

- 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 section 5.1)

Upon request of the applicant the indication of the reference medicinal product in severe aplastic anaemia is currently omitted in line with Article 11 of Directive 2001/83/EC and Article 3.3(b) of Regulation No 726/2004 as this indication is covered by patent law.

There are no quality issues which need to be addressed and the product can be considered acceptable.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

Eltrombopag Viatris film-coated tablets, 75 mg, is bioequivalent with Revolade 75 mg film-coated tablets based on the presented clinical study under fasting conditions.

The results of this study with 75 mg formulation can be extrapolated to other strengths (50 mg, 25 mg and 12.5 mg) according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6. Approval is recommended from the clinical point of view.

The application contains adequate quality data and the bioequivalence has been shown.

Upon request of the applicant the indication of the reference medicinal product in severe aplastic anaemia is currently omitted in line with Article 11 of Directive 2001/83/EC and Article 3.3(b) of Regulation No 726/2004 as this indication is covered by patent law.

A benefit/risk ratio comparable to the reference product can be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Eltrombopag Viatris is favourable in the following indications:

Eltrombopag Viatris is indicated for the treatment of:

- adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

- 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 sections 4.2 and 5.1).

- 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 sections 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.