30 January 2025
EMA/55246/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eltrombopag Accord

International non-proprietary name: eltrombopag

Procedure No. EMEA/H/C/006459/0000

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
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CMS	Concerned Member State
CoA	Certificate of Analysis
COSY	Correlation spectroscopy
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DL	Detection Limit
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
FDA	Food and Drug Administration
FID	Flame ionisation detection
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IR	Infra-red
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection
LoQ	Limit of Quantitation
MAH	Marketing Authorisation holder
MDD	Maximum daily dose
MS	Mass spectroscopy
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
OPA	Oriented Polyamide
PDA	Photo diode array
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
PXRD	Powder X-ray diffraction
QbD	Quality by design
QL	Quantitation limit
QOS	Quality Overall Summary
QTPP	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
SmPC	Summary of Product Characteristics
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 Accord Healthcare S.L.U. submitted on 11 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Eltrombopag Accord, 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 9 November 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 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 Accord is indicated for the treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
>
> Eltrombopag Accord 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).
>
> Eltrombopag Accord 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.

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 number:

  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: 2010-03-11
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s):

  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): 20-VIN-0434

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 (SA) from the CHMP. The applicant sought SA from the Dutch regulatory Agency.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Hjalti Kristinsson

The application was received by the EMA on	11 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	n/a
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	05 October 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	20 November 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	19 December 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	15 January 2025
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 Accord on	30 January 2025

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 Accord 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 applicant applied for the following indications:

- treatment of adult patients with primary immune thrombocytopenia (ITP) who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
- treatment of paediatric patients aged 1 year and above with primary immune thrombocytopenia (ITP) lasting 6 months or longer from diagnosis and who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).
- in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

Upon request of the applicant the indication of the reference medicinal product:

- 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

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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing eltrombopag olamine equivalent to 12.5 mg, 25 mg, 50 mg, and 75 mg eltrombopag as active substance.

Other ingredients are:

Tablet core: mannitol, povidone (K 29/32), cellulose, microcrystalline, sodium starch glycolate (type-A), magnesium stearate, isomalt (E 953), and calcium silicate

Tablet coating: hypromellose (2910) 5mPas, titanium dioxide (E171), triacetin, iron oxide red (E172), iron oxide yellow (E172) [except for 75 mg].

The product is available in aluminum 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 active substance is 3'-{(2Z)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene] hydrazino}-2'-hydroxy-3-biphenylcarboxylic acid-2-aminoethanol (1:2) corresponding to the molecular formula $C_{25}H_{22}N_4O_4$ .2(C_2H_7NO). It has a relative molecular weight of 564.65 and the following structure:

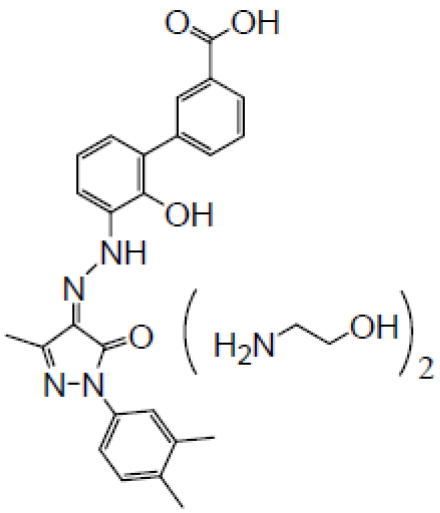

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of UV, IR, ^{1}HNMR, ^{13}C NMR, COSY, HSQC, mass, elemental analysis. The solid state properties of the active substance were measured by PXRD.

The active substance is a red to brown, non-hygroscopic crystalline solid, sparingly soluble in dimethyl sulfoxide (DMSO). Furthermore, eltrombopag olamine is insoluble in aqueous buffers in the physiological range (below 0.02 mg/mL).

Eltrombopag olamine exhibits polymorphism; however, the manufacturing process consistently results in Form I. No conversion of the polymorphic form during the manufacturing process and stability studies was observed.

No chiral centre is present in eltrombopag olamine. Therefore, it does not exhibit stereo isomerism. As per literature it exists as the Z-isomer.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Satisfactory GMP documentation has been provided.

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

Well defined starting materials with acceptable specification are used. Overall, the proposed starting materials are considered to comply with the requirements of ICH Q11. Five (branch 1) and 3 (branch 2) chemical transformation steps in the sense of ICH Q11 separate the proposed starting materials from the final active substance, which is considered sufficient to ensure that impurities generated in the manufacturing process of the starting material do not impact the impurity profile of the final active substance, consistently leading to active substance of appropriate quality.

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

Eltrombopag olamine is packed in double LDPE bags (outer black) and stored inside an HDPE drum. The container closure system complies with EC 10/2011 as amended.

Specification

The active substance specification applied by the finished product manufacturer includes tests for: appearance (visual), identity (IR, HPLC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC, HPLC), impurities (HPLC), assay (HPLC), content of olamine (Potentiometric Titration), microbiological contamination (Ph. Eur.) and particle size distribution (Ph. Eur.).

The specification for the active substance by the finished product manufacturer is identical to the specification presented by the active substance manufacturer in the ASMF, with the addition of tests for microbiological contamination and particle size distribution.

The maximum daily dose (MDD) for eltrombopag is 150 mg/day. Therefore, the ICH recommended thresholds for reporting, identification and qualification in the active substance are 0.05%, 0.10% and 0.15%, respectively. The specified and unspecified impurities are controlled in-line with the requirements of ICH Q3A. This is acceptable.

The amino Impurity (U/1103, i.e. 3'-amino-2'-hydroxybiphenyl-3-carboxylic acid) shows a structural alert for mutagenicity (aniline derivative). A bacterial reverse mutagenicity test (Ames test) was performed on U/1103 in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537, as well as Escherichia coli WP2uvrA, in the absence and presence of rat S9 metabolic activation up to a concentration of 5000 µg/plate. There was no test-item related increase in the number of revertant under any condition. Hence, control of U/1103 (amino impurity) in-line with ICH Q3A is deemed justified.

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 testing has been presented.

Batch analysis data (n=6 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

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

The following parameters were tested*:* description, identification (IR and HPLC), water content (KF), related substances (HPLC) and assay (HPLC). The analytical methods used were the same as for release and were stability indicating.

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.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months stored in well closed containers between 20-25 °C (excursions are allowed between 15-30 °C) 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: Orange to brown, round, biconvex film-coated tablet with "I" debossed on one side and with a diameter of approximately 5.5 mm.

25 mg: Dark pink, round, biconvex film-coated tablet with "II" debossed on one side and with a diameter of approximately 8 mm.

50 mg: Pink, round, biconvex film-coated tablet with "III" debossed on one side and with a diameter of approximately 10 mm.

75 mg: Red to brown, round, biconvex film-coated tablet with "IV" debossed on one side and with a diameter of approximately 12 mm.

The finished product was developed as a generic equivalent to the reference medicinal product Revolade. Consequently, the development objective was to prepare a film-coated tablets being essentially similar to the reference medicinal product. The product is intended as an immediate release product with a comparable dissolution profile to the reference and acceptable pharmaceutical stability.

A risk assessment of the active substance quality attributes was performed to evaluate the impact that each attribute could have on the finished product critical quality attributes (CQAs). Eltrombopag is insoluble between pH 1.2 and 6.8.

Particle size of the active substance was investigated during pharmaceutical development as it may impact dissolution and bioavailability. The influence of particle size was investigated by means of dissolution profiles and a pilot bioavailability study. The finished product containing the active substance with a small particle size dissolved faster compared to finished product containing active substance with larger particles. However, the corresponding bioavailability data demonstrated that active substance particle size has no impact in vivo.

Incompatibilities between the active substance and the excipients have not been found in literature, nor have been observed during the stability studies.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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 pharmaceutical development of the finished product uses a Quality by Design (QbD) approach, however, no design space is claimed by the applicant.

Quality Target Product Profile (QTPP) of the finished product is based on the clinical and pharmacokinetics properties, *in vitro* dissolution profile, physicochemical characteristics of the reference medicinal product. The quality target product profile (QTPP) was defined based on characterization of the reference product, the properties of the active substance, the intended patient population and intellectual property restrictions. Risk assessment was used throughout development to identify potentially high risk formulation and process variables, and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated during or after development to capture the reduced level of risk based on knowledge gained through development.

The FDA's recommended dissolution method published for Eltrombopag tablets was the starting point for the development of the analytical method for routine release testing of the finished product. The discriminatory power of the proposed dissolution method was investigated to support its choice for batch-to-batch quality control. The selection of the parameters to be evaluated was based on the outcome of the risk assessment of the formulation and manufacturing process variables that can affect the dissolution of the finished product. The discriminative power of the proposed QC dissolution method could not be fully demonstrated by the implemented single changes to the formulation and manufacturing parameters. Only a combination of changes resulted in a significant decrease in release. However, taking also into consideration that the proposed QC dissolution method detected differences in formulation between the test and reference 75 mg biobatches, resulting in similarity factors below 50, the method is deemed sufficiently discriminative for routine use.

A bioequivalence study was performed on the 75 mg strength showing bioequivalence between the generic formulation and the reference medicinal product formulation.

A biowaiver for the lower 12.5 mg, 25 mg and 50 mg strengths on the basis of the successful "fasting" bioequivalence study was proposed. In support, dissolution data was provided in three different release media with and without the addition of a surfactant for all strengths of the test product. Overall, similar dissolution profiled between strengths are obtained. The conditions for granting a biowaiver are, therefore, considered fulfilled and no further bioequivalence studies for the lower strengths are considered necessary.

The manufacturing development strategy was to design and develop a generic medicinal product using commonly used excipients similar to the reference product. A common blend approach for the manufacture of all four strengths was proposed, using a wet granulation process consisting of the following individual steps: wet granulation, drying, milling, mixing, lubrication, compression, and Film-coating.

The results of an initial risk assessment on the various manufacturing steps in terms of their potential impact on the finished product CQAs were provided. Previous experience was used to determine the degree of risk associated with each process step and its effect on the finished product.

Confirmatory batches of the finished product have been manufactured in order to assess the suitability of the proposed manufacturing process parameters during the scale up. Two batches were manufactured according to proposed process parameters for the granulation, drying, milling, blending, compression and coating steps. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria.

The primary packaging is aluminum 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 is a simple wet granulation process, followed by compression and film-coating of the cores. The manufacturing process consists of 6 main steps: blending, granulation, milling, drying, tabletting and coating. 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 include appropriate tests for this kind of dosage form: description (visual), identification (UV, HPLC), assay (HPLC), related substances (HPLC), dissolution (In House) and uniformity of dosage units (Ph. Eur.)

The maximum daily dose (MDD) for Eltrombopag film-coated tablets is 150 mg/day. Therefore, the required thresholds by ICH for reporting, identification and qualification in the finished product are 0.1%, 0.2% and 0.2%, respectively. The proposed control limits for unspecified impurities are in-line with ICH Q3B and hence acceptable. The limit for total impurities in the finished product corresponds to the acceptable limit for total impurities in the active substance.

No acceptance criteria for microbial contamination are set. The absence of microbial testing at release and during end-of-shelf life is justified in line with ICH Q6A based on the low water activity of the drug product (< 0.40), as well as the microbial testing results of submission batches at release and during the stability program.

An elemental impurities risk assessment was performed on the finished product as per ICH Q3D Option 2b, i.e. permitted concentration limits of elements in individual components of a product with a specified daily intake. The ingoing active substances, excipients, manufacturing equipment and utilities, as well as packaging components were evaluated as part of the risk assessment. Under Option 2b, Class 1 and Class 2A elemental impurities relevant for the oral route of administration were assessed, as well as the Class 2B elements Au, Ru, Se, Ag, Pt and Pd. The risk assessment demonstrated the total elemental impurity contribution from the finished product components is well below the 30% threshold of the oral Permitted Daily Exposure (PDE) limits published in ICH Q3D for each element. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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. During evaluation the CHMP requested as Major Objection (MO) to include risk evaluation document and the CMDh template for nitrosamine evaluation in Module 1.0. The applicant confirmed that these documents were provided at the time of submission in Module 1. The response was considered satisfactory and the issue is resolved.

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 twelve commercial scale batches of Eltrombopag film-coated tablets (three batches of each strength batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 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.

A bulk stability study of four batches stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were also provided

Samples were tested for appearance, assay, impurities, dissolution, and microbial quality. Furthermore, one batch of each strength was tested for water activity. The analytical procedures used are stability indicating.

The finished product is generally very stable in the proposed container packaging system and no general trends or signs of degradation are observable when stored under long term and accelerated conditions. Unspecified and total impurities remain below the reporting threshold (0.1%) and no change in dissolution and assay is noticed during the time-frame covered under both storage conditions. Due to the high water vapor barrier of the primary packaging material, water uptake during stability is not considered a risk.

A photostability study has been performed on neat film-coated tablets, as well as drug product wrapped and protected by Al-foil. The conditions of the study were selected according to ICH Q1B. The drug product did not show signs of degradation after exposure to light without the protection of the primary and/or secondary packaging materials. The finished product was hence not considered to be photosensitive.

Based on available stability data, the proposed shelf-life of 2 years without storage conditions as stated in the SmPC (section 6.3 and 6.4) 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.

During the procedure one MO had been raised related to the risk evaluation documentation for nitrosamine evaluation. The MO was resolved by provision of the requested documents.

The applicant has applied QbD principles in the development of the active substance and/or 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.

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.

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. Eltrombopag is a widely used and well-known active substance, and in addition to literature review the applicant has provided additional study, a Bacterial Reverse Mutation Assay study with the impurity aminophenol-eltrombolate (U/1103) which was formed during the synthesis of eltrombopag. The purpose of the study was to evaluate the mutagenic potential of U/1103. No mutagenic activity of U/1103 was found. The overview is adequate and 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 studies were submitted. This was justified by the applicant as the introduction of Eltrombopag Accord manufactured by Accord Healthcare S.L.U. 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 SmPC are in line with the SmPC of the brand leader product. A non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The application contains an adequate review of published non-clinical data. The impurity profile has been discussed and was considered acceptable. Omission of Environmental Risk Assessment is justified.

2.3.4. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film coated tablets containing eltrombopag. To support the marketing authorisation application the applicant conducted 1 bioequivalence study with the 75 mg strength and a 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 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.

The clinical-, bioanalytical- and statistical sites have been inspected by EU authorities according to the list of inspections provided. No open issues remain following a 2023 inspection of the bioanalytical site by the leading EU authority.

Exemption

A strength based biowaiver is applied for the additional strength 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 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 PhEq. 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.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study, no.20-VIN-0434.

Table 1: Tabular overview of clinical studies

Study No	Study title
20-VIN-0434	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Eltrombopag 75 mg film-coated tablets and Revolade 75 mg film-coated tablets (containing eltrombopag) in healthy, male and female volunteers under fasting conditions.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study no: 20-VIN-0434

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Eltrombopag 75 mg film-coated tablets and Revolade 75 mg film-coated tablets (containing eltrombopag) in healthy, male and female volunteers under fasting conditions.

Methods

- **Study design**

The study was an open label, balanced, randomized, two treatment (Test (T) and Reference (R)), two-sequence, two-period, single-dose, crossover bioequivalence study in 64 healthy adult, human male & female subjects under fasting conditions.

- **Test and reference products**

Treatment	
Test Product	Eltrombopag film-coated tablets, 75 mg Manufactured by: Synthon Hispania, S.L., Spain
Reference Product	Revolade (Eltrombopag) 75 mg film-coated tablets MAH: Novartis Europharm Limited, Ireland. Batch No. BTP28A Expiry Date Feb 2023

- **Population(s) studied**

Sixty-four (64) healthy adult subjects were planned to be enrolled in the study however a total of sixty-two (62) healthy adult subjects were enrolled and dosed in the study (15 females and 47 males; 20-44 years, BMI 18.68-29.41 kg/m^2) and dosed in period 1. Sixty (60) subjects were dosed in period 2 (two subjects withdrew their consent). Total of sixty (60) subjects completed the study and were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

The method validation was completed at 12 Oct 2017, before onset of the bioanalytical phase of the study. Amendments up until amendment 4 were completed before the bioanalytical phase of the study. Amendment 5 was performed after the bioanalytical phase (and included analysis of effects of metabolite on eltrombopag quantification).

Calibration range: 0.050 µg/mL to 30.000 µg/mL

QC concentrations (µg/mL): 0.050 (LLOQ), 0.150 (LQC), 3.600 (MQC-2),9.000(MQC-1),

22.500 (HQC) and 140.000 (DQC)

Data acquisition and data integration were done using Analyst software Version 1.6.3

The bioanalytical report, dated 28 Aug 2021 is provided.

During bioanalysis, accuracy and precision values of QC samples are:
Accuracy: 101.43% to 105.33%, Precision: 2.18 % - 2.53 %, which is in line with values in the validation rapport. QC samples were the same as used during method validation.

Total number of samples analysed: 2671 samples
Storage temperature: -78 ± 8°C
Analysis of study samples: 28 May 2021 to 19 Jun 2021
Duration of sample storage until completion of analysis: 56 days from the first sample collection to the last sample analysis (eltrombopag long term stability in human plasma under storage conditions has been proved for 63 days).

Repeat analysis: 280 samples (176 analytical batch failure, 14 inconsistent ISTD area, 88 sample lost during analysis, 2 due to baseline value in pre-dose sample)

Incurred Sample Reanalysis (ISR): ISR was performed in 184 samples out of 2671 samples for eltrombopag in order to evaluate the incurred sample reproducibility; 184 (100%) samples out of 184 samples were within acceptance criteria.

- **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**

For Eltrombopag, the ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} were analyzed by analysis of variance (ANOVA) using PROC GLM in SAS Software, Version 9.4.

The model statement of PROC GLM in SAS Software included the fixed effects of Sequence, Treatment, Period and Subject (Sequence). The Sequence effect was tested using the Subject (Sequence) effect as the error term.

Results

Table 2: Pharmacokinetic parameters for Eltrombopag (non-transformed values)

Pharmacokinetic parameter	**Test (N=60)**	**Reference (N=60)**
	arithmetic mean ± SD	**arithmetic mean ± SD**
$AUC_{(0-72h)}$ (µg/mL) *(hr)	151.295±47.4572	152.801±50.5423
C_{max} (µg/mL)	14.428±3.4095	14.179±3.6149

Pharmacokinetic parameter	Test (N=60)	Reference (N=60)
	arithmetic mean ± SD	arithmetic mean ± SD
T_{max}*	3.000 (1.50-5.50)	3.500 (3.500-6.00)

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 3: Statistical analysis for Eltrombopag (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%
AUC $_{(0-72)}$ (h*µg/mL)	99.85	94.13 – 105.91%	19.51
C_{max} (µg/mL)	102.17	96.33 – 108.36%	19.46

- **Safety data**

A total of six (06) adverse events were reported by four (04) subjects during the study. All AEs were mild in severity and reported after the single dose administration. Three (03) adverse events were reported by three subjects (03) following administration of reference product. Three (03) adverse events were reported by two (02) subjects following administration of test product.

There were six (06) AEs (Burning sensation, Vomiting, Increased Ventricular rate, Increased QTc Interval, Abdominal pain and Chest pain) which were considered related to the reference/test product. One subject was withdrawn from the study due to vomiting in period 01 after administration of the reference product on 25 Apr 2021 which was resolved the same day.

2.4.2.2. Pharmacodynamics

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

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety of eltrombopag is adequate. 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.

For products where the general biowaiver criteria of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr** is fulfilled, it is usually sufficient to establish bioequivalence with only one strength, which is determined by the linearity in pharmacokinetics of the active substance.

The biowaiver request for additional strengths is considered justified since PK linearity in the dose range 12.5-75 mg has been established.

Tabular in vitro dissolution data of 12 units including individual values, mean values and RSD (%) of the investigated products have been provided in M2.7.1 and 3.2.P.2.2.

Eltrombopag demonstrates pH-dependent solubility, with no solubility in HCL 0.1N and at pH 4.5 acetate buffer and low solubility at pH 6.8 phosphate buffer. For biowaiver purposes, the dissolution data at pH 6.8 phosphate buffer without surfactant is considered.

To support this application, the applicant submitted one bioequivalence study, no. 20-VIN-0434. The study was an open label, balanced, randomized, two-treatment, two sequence, two-period, single-dose, crossover oral bioequivalence study of Eltrombopag 75 mg film-coated tablets and Revolade 75 mg film-coated tablets (containing eltrombopag) in healthy, male and female volunteers under fasting conditions. A total of sixty-two subjects (62) were enrolled and dosed in Period 1, in line with the protocol. Sixty (60) subjects completed the study and were included into 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 no. 20-VIN-0434 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_{0-72} 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 (20-VIN-0434) 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 Accord film-coated tablets, 75 mg is bioequivalent with Revolade 75 mg film-coated tablets based on the presented study no. 20-VIN-0434 under fasting conditions.

The results of study 20-VIN-0434 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.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 4: 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, and 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, and 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.

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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 12.5/25/50/75 film-coated tablets and Solifenacin succinate 5/10 mg film-coated tablets. 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical 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 was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Eltrombopag Accord 75 mg film coated tablets met the protocol-defined criteria for bioequivalence when compared with Revolade 75 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters $AUC_{0\text{-}72h}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two

formulations was demonstrated.

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, section 4.1.6. Approval is recommended from the clinical point of view.

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

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that 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 Accord is favourable in the following indications:

- Eltrombopag Accord 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 Accord 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 Accord 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).

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.