15 September 2022
EMA/CHMP/805980/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Teriflunomide Accord

International non-proprietary name: teriflunomide

Procedure No. EMEA/H/C/005960/0000

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List of abbreviations

°C	Degree centigrade
AE	Adverse event
ANOVA	Analysis of variance
ASMF	Active substance master file
AUC	Area under the curve
BLQ	Below limit of quantitation
C_{max}	Maximal plasma concentration
CQA	Critical quality attribute
CU	Content uniformity
CV	Coefficient of variation
DOE	Design of experiments
DQC	Dilution quality control
DSC	Differential scanning calorimetry
EMA	European medical agency
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
HQC	High quality control
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IPA	Isopropyl alcohol
IR	Infrared
ISR	Incurred sample reanalysis
K_2EDTA	Dipotassium ethylene diamine tetra acetate
KF	Karl Fisher
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LLOQ	Lower limit of quantification
LMQC	Low medium quality control
LQC	Low quality control
MO	Major objection
MQC	Medium quality control
MS	Multiple sclerosis
ng/mL	Nanogram per millilitre
NMR	Nuclear magnetic resonance
No.	Number
PPCP	Polypropylene copolymer
PVC	Polyvinyl chloride
QA	Quality assurance
QbD	Quality by design
QC	Quality control
QTPP	Quality target product profile
RH	Relative humidity
RMP	Risk management plan
SOP	Standard operating procedure
T_{max}	Time to maximum plasma concentration

ULOQ	Upper limit of quantification
UV	Ultraviolet
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 8 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Teriflunomide 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 24 June 2021.

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 indication:

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). (please refer to section 5.1 for important information on the population for which efficacy has been established).

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 Aubagio 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 8 years in the EEA:

- Product name, strength, pharmaceutical form: Aubagio 14 mg film-coated tablets
- Marketing authorisation holder: Sanofi-aventis groupe, France
- Date of authorisation: 26.08.2013
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/13/838/001-005

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

- Product name, strength, pharmaceutical form: Aubagio 14 mg film-coated tablets
- Marketing authorisation holder: Sanofi-aventis groupe, France
- Date of authorisation: 26.08.2013
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/13/838/001-005

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: Aubagio 14 mg film-coated tablets
- Marketing authorisation holder: Sanofi-aventis groupe, France
- Date of authorisation: 26.08.2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/838/001-005

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 appointed by the CHMP were:

Rapporteur: Nevenka Trsinar Brodt

The application was received by the EMA on	8 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions	27 June 2022

to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	10 August 2022
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	31 August 2022
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 Teriflunomide Accord on	15 September 2022

2. Scientific discussion

2.1. Introduction

This application for the marketing authorisation of Teriflunomide Accord 14 mg film-coated tablets was submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. The reference medicinal product is Aubagio 14 mg film-coated tablets marketed by Sanofi Aventis Groupe, France, authorised in the EU on 26th August 2013 via the centralised procedure (EMEA/H/C/002514).

The reference product is also authorised as 7 mg film-coated tablets however, this strength has not been applied for with the proposed generic product.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on *de novo* synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis (MS) is not fully understood, but this is mediated by a reduced number of T-lymphocytes.

Pharmacotherapeutic group:

Immunosuppressants, Selective immunosuppressants, ATC Code L04AA31

Proposed indication:

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). *(please refer to section 5.1 for important information on the population for which efficacy has been established).*

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 14 mg of teriflunomide.

Other ingredients are:

Tablet core: lactose monohydrate, maize starch, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica, hydroxypropylcellulose, magnesium stearate;

Tablet coating: hypromellose (E464), titanium dioxide (E171), talc (E553b), macrogol (E1521), indigo carmine aluminum lake (E132).

The product is available in aluminium-aluminium blisters packed in cartons, and aluminium-aluminium perforated unit-dose blisters packed in cartons, as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of teriflunomide is (2Z)-2-cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]but-2-enamide corresponding to the molecular formula $C_{12}H_9F_3N_2O_2$. It has a relative molecular mass of 270.21 and the following structure:

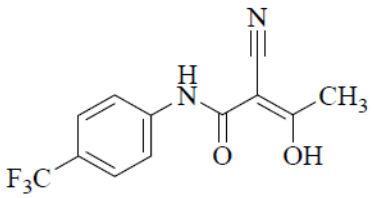

Figure 1: Active substance structure

The chemical structure of teriflunomide was elucidated by a combination of IR, UV, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, mass spectroscopy and elemental analysis. The solid-state properties of the active substance were measured by XRPD data and DSC tests.

The active substance is a white or almost white powder, slightly hygroscopic, practically insoluble in water, in buffers pH 1.2, pH 4.0 and pH 7.0, and in methanol.

Teriflunomide contains no asymmetric centre, therefore no enantiomers are possible. Single crystal X-ray diffraction (XRD) and DSC analysis studies have demonstrated that teriflunomide recrystallised from different solvents results in one and the same crystalline form. The form is consistent between batches synthesised with the proposed commercial process, and is stable during storage as confirmed by XRD analyses in stability studies.

Ph. Eur. monograph was published recently for teriflunomide (07/2021:3036).

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by a single manufacturer, which is also the finished product manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Teriflunomide is synthesised in four main chemical transformation steps and one salt formation.

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.

The active substance is packaged in double transparent polyethylene bag and then in triple laminated bag. This is finally placed in HDPE drum. The primary packaging material complies with EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: description, solubility (Ph. Eur.), identification (IR), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (coulometry), and sulfated ash (Ph. Eur.), particle size (Laser diffraction) and microbial limit test (Ph. Eur.).

The proposed specification is acceptable since it includes all relevant parameters and limits and is in line with ICH guidelines and Ph. Eur. requirements.

Only one impurity is specified in the Ph. Eur. monograph. In the proposed specification additional in-house impurities are specified. The specification limit for total impurities has been tightened as requested, and the active substance specification is now in line with the Ph. Eur. monograph.

The residual solvent limits are aligned with ICH Q3C. The specification of the solvents includes a limit for the potential contaminant benzene.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. In-house methods are used for the control of assay, related substances, residual solvents and particle size. Comparison of the in-house and Ph. Eur. method for related substances and for assay was provided. The use of in-house methods is sufficiently justified. The method for water content has been changed to Ph. Eur. method 2.5.32 to align with the Ph. Eur. monograph for teriflunomide.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance were provided. The results are within the specifications and consistent.

2.2.2.4. Stability

Stability data from three process validation 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 (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, water, related substances and assay. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no trends or significant changes were observed. There was no conversion of polymorphic form.

Photostability testing following the ICH guideline Q1B was performed on one batch and demonstrated that the active substance is not sensitive to light.

Results on stress conditions (acid degradation, alkali degradation, oxidation degradation, thermal degradation, UV and fluorescence light degradation, humidity degradation) were also provided on one batch, and demonstrated that the active substance is sensitive to acid, alkali and oxidative degradation.

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 36 months in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Teriflunomide film-coated tablets are blue coloured, pentagonal shaped, debossed with "T2" on one side and plain on other side. The tablets are packed in aluminium-aluminium blisters.

The finished product has been developed to be a generic equivalent to the reference medicinal product Aubagio 14 mg film-coated tablets. The quality target product profile (QTPP) was defined as an immediate release film-coated tablet for oral administration, containing 14 mg of teriflunomide, bioequivalent to the reference medicinal product, and meeting the same or compendial or other relevant quality standards, packaged in a suitable container closure system which allows at least 24 months shelf-life at room temperature.

The critical quality attributes identified were assay, content uniformity (CU), dissolution and degradation products.

A risk assessment of the active substance attributes was performed to evaluate the impact on the finished product CQAs.

The active substance particle size specification was aligned with the particle size of the active substance batch used in the bioequivalence study, as requested. Only one active substance crystalline form has been identified in the active substance studies. Stability of polymorphic form of active substance during finished product manufacturing and during storage has been demonstrated.

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 excipients used in teriflunomide tablets were selected based on excipients used in the reference product composition and based on the excipient compatibility studies.

The formulation difference to the reference medicinal product is considered not to be significant, and the composition of the intended commercial formulation is acceptable.

The formulation was optimised using Design of Experiments (DOE). Based on the results of DOE trials, it was concluded that there is only a low risk that the studied formulation variables would affect any finished product quality attributes.

There are no overages in the formulation.

The applicant has applied QbD principles in the manufacturing development of the finished product. However, no design spaces were claimed for the manufacturing process of the finished product.

Critical process steps have been identified and risk assessment performed on potential impact of process on finished product critical quality attributes. The manufacturing process consists of weighing, milling, granulation and drying, blending and lubrication, compression, and film-coating. Based on the results of process optimisation study, the control strategy for critical process parameters has been defined.

A bioequivalence study was conducted under fasting condition to compare the pharmacokinetic profile and bioequivalence of teriflunomide film-coated tablets 14 mg with the reference product AUBAGIO® 14 mg film-coated tablets.

The results of in vitro dissolution tests at three different buffers (pH 1.2, 4.5 and 6.8-QC media) obtained with the batches of test and reference products that was used in the bioequivalence study have been provided. Dissolution profiles are comparable in all dissolution media (visual comparison done for pH 1.2 and 4.5, f2 statistics done for pH 6.8).

The dissolution method has been developed considering the solubility profile and sink conditions of teriflunomide. Discriminatory power of the dissolution method at the specification limit has been demonstrated towards slight changes to the composition. Additional assessment of discriminatory power of dissolution method towards modified process parameters has been performed as requested. Discriminatory power of the dissolution method at the specification limit has been demonstrated, also towards modified hardness parameters.

There are no differences in the manufacturing processes or formulation composition of the commercial product and clinical trial material.

The primary packaging is aluminium-aluminium blisters. 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.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of wet granulation followed by compression and film coating. The main manufacturing steps are: raw material sifting, binder solution preparation, dry mixing, granulation, drying, sizing, blending and lubrication, compression and film-coating. The process is considered to be a standard manufacturing process. A single tablet manufacturing site is being proposed, and multiple primary and secondary packaging sites.

During the procedure, a Major Objection (MO) was raised related to GMP documentation deficiencies for one of the proposed secondary packaging sites. The applicant consequently removed the concerned site from the dossier.

Process controls of critical steps (blending and lubrication, compression, film coating and packaging) together with test methods and acceptance criteria were described and are considered acceptable.

Major steps of the manufacturing process have been validated by a number of studies on three consecutive production scale batches. 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 and pharmaceutical form.

Hold times proposed for manufacturing process intermediates and for the bulk product were acceptable.

2.2.3.3. Product specification(s)

The finished product release specifications include tests for: description (visual), average weight of tablets (weighing), identification for teriflunomide (HPLC, UV), identification for colorants (colour test), water content (Ph. Eur.), dissolution (Ph. Eur.), uniformity of dosage units by content uniformity (Ph. Eur.), assay (HPLC), related substances (HPLC), microbial enumeration (Ph. Eur.), test for specific micro-organism (E. coli) (Ph. Eur.).

The specification parameters are in accordance with Ph. Eur. monograph for tablets and ICH Q6A. Ph. Eur. monograph for teriflunomide tablets was published in Supplement 10.7 (04/2022:3037) and implemented on 1 April 2022.

The specification limit for dissolution was set according to the results of the biobatch (which is in line with the reflection paper Dissolution specification for generic oral immediate release products), and the Ph Eur monograph for teriflunomide tablets. The limit is appropriate and accepted.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was initially assessed as not sufficiently comprehensive, and a MO was raised. The applicant responded adequately by providing a revised nitrosamine risk assessment, together with confirmatory test results for nitrosamine impurities in finished product batches.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Equivalence between the in house and the Ph. Eur. methods for assay and related substances has been demonstrated.

Satisfactory information regarding the reference standards used for assay, impurities and dissolution testing has been presented.

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

2.2.3.4. Stability of the product

Stability data from three commercial scale batches 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 (40°C / 75% RH) according to the ICH guidelines were provided. The batches of teriflunomide film-coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the shelf-life specifications. The analytical procedures used are the same as those used for release testing and are stability indicating.

All results are within the proposed limits. At the accelerated and long-term storage conditions there is a slight increase of specified impurity and total impurities. However, the results are well within the specification limits and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, samples form one commercial scale batch were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product was exposed unpacked, in the immediate pack and in the marketing pack. Based on the results of photostability study it can be concluded that the finished product is photostable.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions as stated in the SmPC (section 6.3 and section 6.4) are acceptable.

2.2.3.5. Adventitious agents

The applicant confirmed that the lactose monohydrate is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other 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, two quality MOs were raised, one related to inadequate GMP evidence of a proposed packaging site, and one related to the nitrosamine risk assessment, which was not comprehensive enough. The applicant responded adequately by removing the concerned packaging site from the dossier, and by providing a revised nitrosamine risk assessment, together with confirmatory test results for nitrosamine impurities in finished product batches.

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. Recommendation(s) 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

As this was a generic application, no Environmental Risk Assessment (ERA) studies were submitted. However, the API consumption data for the period between 2018 and 2021 showed an increase in total teriflunomide consumption in the past. Therefore, these data were used for the calculation of refined F_{pen} and refined $PEC_{surfacewater}$, which is below the trigger value for the Phase II assessment. Also, as shown in the assessment report of the reference product, Aubagio, teriflunomide is not persistent, bioaccumulative nor toxic, and the log K_{ow} does not exceed the trigger value. Hence, Teriflunomide Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to cause any significant risk to the environment.

2.3.3. Discussion on non-clinical aspects

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 was discussed during the application and the impurity specifications were narrowed to be in line with Ph. Eur. monograph for teriflunomide.

Additional information on teriflunomide environmental risk assessment consumption data for teriflunomide for the period for years 2018-2021 was submitted during the application. The refined $PEC_{surfacewater}$ was calculated which is below the trigger value for the Phase II assessment. Also, as presented in the assessment report of the reference product Aubagio, teriflunomide is not a PBT substance, and the log K_{ow} does not exceed the trigger value.

Therefore, the CHMP concluded that teriflunomide is unlikely to result in any significant increase in the combined sales volumes for all teriflunomide containing products and the exposure of the environment to the active substance. The absence of a complete environmental risk assessment is considered justified for the present application.

2.3.4. Conclusion on the non-clinical aspects

The CHMP concluded that the non-clinical information submitted as part of this application supports the use of Teriflunomide Accord in the approved indication.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing teriflunomide. To support the marketing authorisation application the applicant conducted one bioequivalence study with parallel design under fasting conditions.

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.

It should be noted that only film-coated tablets with a dose strength of 14 mg are being applied for in this application, whereas the reference product is registered for both 7 mg and 14 mg dose strength.

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.

Tabular overview of clinical studies

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

Type of study	Study Identifier	Location of Study Report	Objective(s) of the study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	0871-16	• m5-3-1-2-vol 1 of 4 • m5-3-1-2-vol 2 of 4 • m5-3-1-2-vol 3 of 4 • m5-3-1-2-vol 4 of 4	An open label, balanced, randomized, two-treatment, single-period, single oral dose, parallel bioequivalence study of two products of Teriflunomide tablets 14 mg in normal, healthy, adult, human, male subjects under fasting condition.	Single-period, single oral dose, randomized, two-treatment, bioequivalence study, fasting condition.	Teriflunomide film-coated tablets 14mg, Single dose, Oral	79	Healthy, Adult, Human subjects	Single dose	Complete ; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 0871-16: An open label, balanced, randomized, two-treatment, single-period, single oral dose, parallel bioequivalence study of two products of Teriflunomide tablets 14 mg in normal, healthy, adult, human, male subjects under fasting condition

Methods

- **Study design**

Study No. 0871-16 was a single-dose, randomised, single-period, two-treatment, parallel-designed study to investigate the bioequivalence of teriflunomide 14 mg film-coated tablets by Accord, to Sanofi-aventis group's Aubagio film-coated tablets, 14 mg following a single, oral 14 mg (1 x 14 mg) dose administration in healthy male volunteers under fasting conditions.

The study was conducted in two groups in 80 subjects in total. In each group, after an overnight fast of at least 10 hours, a single oral dose (14 mg) of either the test product or the reference product was

administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture. The IMP administration was as per the randomisation schedule and under open-label conditions.

Subject meal requisition forms were submitted by the applicant to provide information on meal distribution (time of administration of meals), and on composition of meals (Standard diet for Lambda Therapeutic Research) during the study.

Following administration of investigational products, the subjects were instructed to consume one sachet containing cholestyramine 4 g three times in a day every 8 hours from Day 4 to 11 or at early termination (discontinuation/withdrawal) of the subject. Measurement of teriflunomide concentration was performed after completion of cholestyramine administration (cholestyramine self-administration by subject) to ensure complete elimination of teriflunomide from the body. In case where teriflunomide plasma concentration was greater than 0.02 mg/L, the subjects underwent additional immediate accelerated elimination procedure (in-house at clinical facility) by administration of cholestyramine.

- **Test and reference products**

Teriflunomide Accord 14 mg film-coated tablets manufactured by Intas Pharmaceutical Limited, India (applicant Accord Healthcare S.L.U., batch No. T01824, manufacturing date February 2016; exp. date January 2018) has been compared to Aubagio 14 mg film-coated tablets manufactured by Sanofi-aventis groupe, France (Batch No: 5H62H, exp. date October 2018).

The applicant has provided signed and dated (3rd May 2022) statement that the quantitative composition and manufacturing process of teriflunomide 14mg film-coated tablets used in bioequivalence study (Project no. 0871-16) is identical to the formulation proposed in the registration dossier.

- **Population(s) studied**

A total of 82 subjects were checked in for the study. Two of 82 subjects were checked in the study, in order to compensate for any dropouts and were checked out of the facility as none of the subjects discontinued / were withdrawn from the study before dosing. Hence, as per the protocol, 80 subjects were dosed in the study.

A summary of disposition of subjects is provided below:

Planned for inclusion	80
Pre-dose discontinued / withdrawn subjects	00
Dosed	80
Post-dose withdrawn / discontinued subjects	05 (test product: N = 2 & reference product: N = 3)
Analysed	80 (in which withdrawn subject no.1069 was also analysed as per the protocol requirement)
Considered for statistical analysis	79 (test product: N = 39 & reference product: N = 40)

Three subjects discontinued from the study on their own accord. Two subjects were withdrawn from the study on medical grounds. 75 subjects completed the clinical phase of the study successfully.

All male subjects included in the study met the inclusion criteria and exclusion criteria described in the study protocol. All the subjects were dosed as per the randomisation.

As per protocol, the pharmacokinetic analysis were performed on the available concentration data of all the subjects. One subject was excluded from statistical analysis since he discontinued from the study and therefore the last three blood samples were not obtained.

Case Report Forms for all discontinued/withdrawn subjects, as well as all subjects, which experienced adverse events during the study have been provided.

- **Analytical methods**

Analysis of study samples and within-study validation

The purpose of study 0871-16 was to measure teriflunomide in the subject samples. The concentrations of teriflunomide in human plasma containing K_2EDTA as an anticoagulant were determined using a selective, reproducible, precise and accurate LC-MS/MS method using teriflunomide-d4 as an internal standard. Moreover, teriflunomide was also measured in screening samples, which were collected on day 12 after administration of cholestyramine for complete elimination of teriflunomide from the body.

The sample analysis was performed at the bioanalytical facility Lambda Therapeutic Research Ltd., Lambda house, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-382481, Gujarat, India. Bioanalytical phase has been performed from 5th June 2017 to 24th June 2017.

Quality assurance statement and statement on GLP, Protocol, Bioanalytical study plan and SOPs of Lambda Therapeutic Research Ltd compliance have been submitted.

2158 subject samples (2077 samples of period I and 81 screening samples) were collected and received at bioanalytical facility in frozen condition in boxes containing adequate amount of dry ice. All received samples were analysed.

Maximal storage period of study samples (24 days at -65±10°C) was within validated long-term stability of teriflunomide in K_2EDTA plasma (71 days at -65±10°C).

The study personnel involved in the sample analysis were kept blinded from the randomisation code during the entire study.

The plasma concentrations of teriflunomide has been determined using LC-MS/MS method was according to method and relevant system bioanalytical SOPs.

Certificates of analysis of reference standard teriflunomide and internal standard teriflunomide-d4 used in study sample analysis have been submitted.

All samples of one subject were analysed together in one analytical run. Accepted analytical runs (20 analytical runs) met analytical run acceptance criteria: Back-calculated concentrations of the calibration curve standards were within acceptance range (± 15% of nominal value for all, except ± 20% for LLOQ). At least 67% of the QC samples and at least 50% at each concentration level were within acceptance criteria (accuracy values of the QC samples within ±15% of the nominal values). The range of precision and accuracy of the back-calculated concentrations of the calibration curve standard points during the study were 0.7% to 2.1% and 97.6% to 102.1% respectively. Mean precision and accuracy of quality control samples were 1.4% to 4.4% and 103.0% to 108.8%, respectively. Coefficient of determination (r2) was more than 0.99 for each accepted analytical run.

25% serially selected subject's chromatograms according to randomisation schedule have been submitted (chromatograms for 20 subjects). SOP Chromatography acceptance criteria, re-injection, integration and reintegration on HPLC and LC-MS/MS data systems LTR.BA-04-01have also been submitted. None of the analytical runs were reintegrated.

Pre-study method validation

The bioanalytical LC-MS/MS method for the quantification of teriflunomide in human plasma (containing K_2EDTA as an anticoagulant) was validated according to in-house SOP. The bioanalytical method followed was as described in the draft method.

It was clarified that no method changes were done in any of the method SOP's version used for method validation and analysis of study samples. All the changes which were incorporated in revised SOP were editorial changes in text of method SOP. Therefore, no partial validation is needed. It is confirmed that the same make and model of LC-MS/MS instrument has been used for method validation and analysis of study samples.

Bioanalytical method validation was performed at the bioanalytical facility Lambda Therapeutic Research Limited, Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad - 382481, Gujarat, India.

Bioanalytical method has been validated according to Guideline on bioanalytical method validation.

Regarding the main validation the following parameters have been validated, in line with the requirements set in the Guideline on bioanalytical method validation (for quantification of teriflunomide): selectivity (including haemolysed and lipaemic plasma, selectivity in presence of co-administered drugs, verification of interfering potential by co-administered drugs), calibration curve (linearity and coefficient of determination), lower limit of quantification (accuracy, precision), accuracy and precision (within-batch and between-batch), dilution integrity (dilution factor 5), matrix effect, reinjection reproducibility and stability (short-term and long-term stock solution stability of teriflunomide and spiking solution stability of teriflunomide at lower and higher level, short-term and long-term stability of internal standard stock and internal standard dilution, verification of analyte stability in human blood, auto sampler/wet extract stability, bench top stability, wet extract bench top stability), signal to noise ratio (within system performance) and carry over. Additionally, the following parameters have also been validated: limit of detection, robustness and ruggedness and mobile phase stability.

Regarding partial validation (addendum I) the remaining parameters required according to the Guideline on bioanalytical method validation have been validated: long term stability of teriflunomide in human plasma, freeze-thaw stability and extended long term stability of solutions (long-term stock solution stability of teriflunomide and spiking solution stability of teriflunomide at lower and higher level, long-term stability of internal standard stock and internal standard dilution).

In partial validation (addendum II) additional parameters were validated: blood stability, matrix effect, robustness and ruggedness.

Regarding selectivity in the presence of concomitant medications used in BE-study 0871-16, it was clarified that the quantification in LC-MS/MS is purely done on the basis of m/z ratio and since parent ion/fragment of cholestyramine resin and other concomitant drugs (mefenamic acid, dicyclomine, sodium bicarbonate, sodium citrate anhydrous, tartaric acid and citric acid) will be different to that of teriflunomide and teriflunomide–d4 (Internal standard) it would not interfere during analysis of teriflunomide and internal standard teriflunomide-d4

- **Pharmacokinetic variables**

Single-dose pharmacokinetic parameters for teriflunomide were calculated using non-compartmental methods. The following pharmacokinetic parameters were determined:

Primary pharmacokinetic parameters: C_{max} and AUC_{0-72}

Secondary pharmacokinetic parameter: T_{max}

The maximum measured plasma concentration (C_{max}) and the time of observing the peak concentration (T_{max}) was calculated from the plasma concentration vs. time profile of the individual subjects.

Actual time-points of the sample collection are used for the calculation of pharmacokinetic parameters.

Pharmacokinetic analysis was performed on all study subject samples.

- **Statistical methods**

All statistical analyses for teriflunomide were be performed using appropriate procedure of SAS Version 9.3 (SAS Institute Inc, USA).

Descriptive statistics were calculated and reported for all pharmacokinetic parameters for teriflunomide.

The ANOVA model included the fixed effect of formulation. The formulation effect was tested at the 0.05 level of significance. According to study protocol, ANOVA model was intended to include group and formulation as fixed effect. If grouping was not to be applied, then ANOVA model would include formulation as fixed effect.

Only non-smoker, Asian male subjects were included in groups of test and reference product. Comparison of age, BMI, height and weight of test and reference product groups has been provided. There were no statistically significant differences between test and reference products groups based on p-values. There were no differences in baseline characteristics (age, body weight, height, BMI, race, sex, smoking status) between test and reference product groups.

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares means between drug formulations were calculated for ln-transformed data of C_{max} and AUC_{0-72} for teriflunomide.

Bioequivalence was concluded when the 90% confidence intervals of geometric least square mean ratio of the test and reference product fell within the acceptance range of 80.00% - 125.00% for ln-transformed C_{max} and AUC_{0-72} of teriflunomide, as per protocol.

Statistical analysis was performed on 79 subjects, per protocol.

Results

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	Arithmetic mean	SD
$AUC_{(0-72h)}$	127358.083	15099.1020	130575.712	19110.9495
C_{max} (ng /mL)	2715.588	327.2142	2978.796	491.2780
T_{max}*	2.500 (0.500 - 5.500)		1.500 (0.500 - 4.500)	
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)				

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	97.9	93.06 - 102.92	13.5
C_{max}	91.8	86.92 - 96.89	14.6
* estimated from the Residual Mean Squares			

The test to reference ratio of geometric LS means and corresponding 90% confidence interval of the C_{max} and AUC_{0-72} were all within the acceptance range of 80-125%.

T_{max} values have been determined, which were comparable between test and reference products.

Concentrations for both reference and test drug in pre-dose time point were BLQ for all study subjects.

No subject reached C_{max} at the first sample time.

Formulation effect was found to be statistically insignificant for ln-transformed pharmacokinetic parameter AUC_{0-72}. However, it was found to be statistically significant for ln-transformed pharmacokinetic parameter C_{max} of teriflunomide. The significant formulation effect might be contributed due to lower sided 90% confidence interval observed in the study for ln-transformed pharmacokinetic parameter C_{max}. As the study met the bioequivalence criteria with respect to C_{max}, this statistical significance may be disregarded.

- **Safety data**

All 80 subjects were included in the safety assessment.

Seven (7) adverse events (AEs) were reported by five (5) subjects during conduct of the study. Out of reported 7 AEs, one (1) AE was reported during post-study safety assessment of the study. Two (2) AEs were reported in subjects after administration of reference product and five (5) AEs were reported in subjects after administration of test product. Six (6) AEs were mild and one (1) AE was moderate in nature.

The causality assessment was judged as possibly related for four (4) AEs, as unlikely related for two (2) AEs and as not related for one (1) AE.

Two adverse events (AEs) led to subject discontinuation on medical grounds: one subject experienced a urinary tract infection, which was deemed mild in severity and possibly related to the administration of study drug (reference product). Another subject was discontinued due to a Plasmodium Vivax infection, assessed as moderate in severity and not related to the study drug (test product). Both subjects recovered.

There were no deaths or other serious AEs over the course of the study.

The other reported AEs were mild in severity and only four AEs (urinary tract infection, pyrexia, mouth ulceration and increase in alanine aminotransferase) were considered possibly related the study drug.

One subject had clinically significant laboratory abnormality during post-study safety assessment (increased alanine aminotransferase). However, he did not report for his AE follow up and was not traceable even after several attempts and hence was considered to be lost to follow up.

Overall, teriflunomide was well tolerated as a single, oral 14 mg dose administered under fasting conditions.

2.4.2.2. Pharmacokinetic conclusion

Bioequivalence (BE) has been shown between the proposed product Teriflunomide Accord 14 mg film-coated tablets and the reference product (Aubagio 14 mg film-coated tablets, Sanofi-aventis groupe, France).

2.4.2.3. Additional data

Dissolution profile of BE batch of European reference product AUBAGIO film-coated tablets 14mg (MAH: Sanofi-aventis groupe, France) is compared with test BE batch teriflunomide film-coated tablets 14 mg:

Media	Apparatus	Volume of dissolution medium	Temperature of dissolution medium	Agitation speed	Sampling schedule
0.1N HCl	Paddle	1000 mL	37 ± 0.5 °C	50 rpm	5, 10, 15, 20, 30 and 45 minutes
pH 4.5 Acetate buffer					
pH 6.8 Phosphate buffer					
Purified water					

Comparative dissolution profiles between biobatches of test and reference product are considered similar in all tested dissolution media.

In the case of pH 4.5 acetate buffer and purified water more than 85 % of teriflunomide from reference and test product is dissolved within 15 minutes.

In 0.1 N HCl and pH 6.8 phosphate buffer f2 value is greater than 50. However, in dissolution media 0.1 N HCl not all conditions in accordance with the Guideline on investigation of bioequivalence are met to evaluate the dissolution similarity using f2 calculation (the relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point). As the released teriflunomide is less than 1% for the reference product and less than 2% for the test product after 45 minutes no additional data on dissolution comparison was requested.

Experimental conditions for in vitro dissolution experiment are in accordance with Guideline on the investigation of bioequivalence, Appendix III and thus acceptable, except volume of dissolution media (1000 mL is used, according to Guideline on the investigation of bioequivalence it should be 900 mL or less). Since in vitro dissolution profiles of test and reference product are only additional data and in vivo data demonstrating bioequivalence of test and reference product prevails over the in vitro dissolution testing no issue was raised.

2.4.2.4. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

To support this application, a single dose, parallel bioequivalence study under fasting conditions was submitted in order to demonstrate bioequivalence with the reference product Aubagio 14 mg film-coated tablets.

The bioequivalence study was conducted under standardised conditions.

According to the SmPC of the reference product, teriflunomide can be taken with or without food. Therefore, the conduct of the single dose study under fasting condition to detect a potential difference between formulations is justified and in accordance with bioequivalence guidelines.

Subject meal requisition forms were submitted by the applicant to provide information on meal distribution (time of administration of meals), and on composition of meals (Standard diet for Lambda Therapeutic Research) during the study. CHMP considered that meals taken after dosing were standardised in regard to composition and time of administration during an adequate period of time.

The study was conducted under fasting conditions, which is acceptable as the drug product can be taken with or without food and the fasting condition is the most sensitive to identify differences between the formulations.

The parallel study design is considered appropriate considering the very slow elimination of teriflunomide.

Sampling period was sufficient and sampling time schedule was considered adequate by CHMP.

Sampling time schedule was considered adequate considering the median t_{max} of reference product Aubagio is between 1 – 4 hours.

Plasma was used as matrix for the evaluation of teriflunomide concentrations, which is acceptable since teriflunomide is extensively bound to plasma protein (>99%) and is mainly distributed in plasma. The measurement of the parent compound (teriflunomide) in plasma is also acceptable, since teriflunomide is moderately metabolised and is the only component detected in plasma.

Blood samples were collected in K_2EDTA tubes at pre-dose (0.00 hours) and at intervals over 72.00 hours after administration of dose, which is sufficient to determine and provide a reliable estimate of the extent of exposure for immediate-release products.

The population chosen is according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98). A total of eighty (80) healthy, adult, male, human subjects were planned for enrolment as per protocol. The subjects were dosed in two Groups as per randomisation, at the same time during period 1. 75 subjects completed the clinical portion of the study.

As per protocol, the pharmacokinetic analysis was performed on the available concentration data of all the subjects. One subject was excluded from statistical analysis since he discontinued from the study and therefore last three blood samples were not obtained. The exclusion of this one subject, from the statistical analysis, is considered acceptable by CHMP and it is in compliance with the relevant guideline (CPMP/EWP/QWP/1401/98) and with the exclusion criteria of the protocol.

Sample size calculation was considered appropriate.

The sampling time deviations are not expected to have any impact on the overall assessment of the study since the actual time was used for computation in pharmacokinetic and statistical analysis.

Adequate information is provided on the test and reference products. The reference product marketed in Germany is a suitable comparator of the generic product. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product.

Data regarding the test and reference product were considered sufficient.

The bioanalytical method (LC-MS/MS) for quantification of teriflunomide (parent drug) in human K_2EDTA plasma samples was pre-study and within study validated according to Guideline on bioanalytical method validation. Structure of analytical run (8 calibration standards, quality control samples in duplicate, study samples, zero samples, and blank samples) was acceptable. The bioanalytical method is considered acceptable for study samples analysis. Handling of samples was adequate.

The reasons provided for reinjection of one analytical run (software error (application hang up)) and one failed analytical run (subject sample analysis did not meet the analytical run acceptance criteria, as ULOQ failed to meet the acceptance criteria) is considered acceptable. Reinjected chromatographic data have been accepted and the analytical run was repeated.

A total 158 samples (representing 7.6% of study samples) were reanalysed. Reason for repeat samples (concentration above highest standard, 2 samples) and reason for repeat analytical run (subject sample analysis did not meet the analytical run acceptance criteria, 156 samples) are according to SOP Repeat analysis and acceptance of results LTR.BA-03-03 and are considered justified. Repeated values have been reported for pharmacokinetic in statistical analysis.

For incurred sample reanalysis 154 samples were considered for ISR evaluation (10% of 1000 study samples + 5% of the 1077 study samples, which is appropriate for studies having samples size >1000).

All incurred samples were found within the acceptance criteria as per SOP LTR.BA-06-02. Results of incurred sample reanalysis confirms the reproducibility of the analytical method.

LLOQ (10.013 ng/mL) is less than 5% of min C_{max} (1998.606 ng/mL for test product and 2038.096 ng/mL for reference product) and therefore acceptable.

Regarding selectivity in the presence of concomitant medications used in BE-study 0871-16, it was clarified that the quantification in LC-MS/MS is purely done on the basis of m/z ratio and since parent ion/fragment of cholestyramine resin and other concomitant drugs (mefenamic acid, dicyclomine, sodium bicarbonate, sodium citrate anhydrous, tartaric acid and citric acid) will be different to that of teriflunomide and teriflunomide–d4 (Internal standard) it would not interfere during analysis of teriflunomide and internal standard teriflunomide-d4. CHMP considered that the above-mentioned concomitant medications do not affect quantification of teriflunomide in study samples.

SOP deviation regarding freeze and thaw stability in main validation does not have impact on validation results since freeze and thaw stability experiment was repeated in the following partial validation (addendum I).

The pharmacokinetic parameters calculated are standard for a single-dose study. Pharmacokinetic analyses were performed on samples from all study subjects, which is in line with the study protocol. The pharmacokinetic variables investigated are in line with the Guideline for the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) and are considered appropriate. In the study with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{0-\infty}$ and residual area do not need to be reported, it is sufficient to report AUC truncated at 72h (AUC_{0-72h}).

The statistical method used for the pharmacokinetic analyses is considered acceptable. The ANOVA model used is adequate for a bioequivalence study. Only Formulation effect was included in the ANOVA model. Since the study drug was administered to both study Groups simultaneously, this is acceptable.

Only non-smoker, Asian male subjects were included in groups of test and reference product. Comparison of age, BMI, height and weight of test and reference product groups has been provided. There were no statistically significant differences between test and reference products groups based on p-values. It is confirmed that there were no differences in baseline characteristics (age, body weight, height, BMI, race, sex, smoking status) between test and reference product groups.

The 90% confidence intervals for ln-transformed pharmacokinetic variables AUC_{0-72h} and C_{max} were within the conventional bioequivalence range of 80.00% to 125.00%, as defined in the study protocol.

Both the formulations (test and reference) were well tolerated during the conduct of the study. There were no deaths or other serious AEs over the course of the study.

There are no observations, which could have raised concerns about the quality or validity of the sampling process or study sample analyses, the analytical method validation or the statistical analysis. There is no concern with regard to the GCP compliance of the study.

The Clinical sections of the SmPC of the proposed product are in accordance with the reference product Aubagio 14 mg film-coated tablets.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study Teriflunomide Accord 14 mg film-coated tablets is considered bioequivalent with Aubagio 14 mg film-coated tablets (Sanofi-aventis groupe, France).

2.5. Risk Management Plan

2.5.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatic effects Hypertension Haematologic effects Infections Acute Pancreatitis
Important potential risks	Teratogenicity Serious opportunistic infections, including PML
Missing information	Long term safety in paediatric patients

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Hepatic Effects	Routine risk minimisation measures: Sections 4.4, 4.3 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	Routine pharmacovigilance activity: As summarized in RMP Part III Specific adverse reaction follow-up questionnaire for 'Hepatic effects. Additional pharmacovigilance activity: None
Hypertension	Routine risk minimisation measures: Sections 4.4 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product.	Routine pharmacovigilance activity: As summarized in RMP Part III No Specific adverse reaction follow-up questionnaire for 'Hypertension'. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	
Haematologic effects	Routine risk minimisation measures: Sections 4.4, 4.3 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	Routine pharmacovigilance activity: As summarized in RMP Part III No Specific adverse reaction follow-up questionnaire for 'Haematologic effects. Additional pharmacovigilance activity: None
Infections	Routine risk minimisation measures: Sections 4.4, 4.3 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product.	Routine pharmacovigilance activity: As summarized in RMP Part III No Specific adverse reaction follow-up questionnaire for 'Infection'. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	
Acute Pancreatitis	Routine risk minimisation measures: Section 4.4 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: As summarized in RMP Part III Specific adverse reaction follow-up questionnaire for 'Acute Pancreatitis'. . Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Teratogenicity	Routine risk minimisation measures: Section 4.3, 4.6 and 5.3 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational Materials (HCP guide andPatients card)	Routine pharmacovigilance activity: As summarized in RMP Part III Specific adverse reaction follow-up questionnaire for 'Teratogenicity'. Structured analyses of cases reporting pregnancy exposure will be submitted regularly, at harmonised submission dates (3-year cycle) synchronised with Teriflunomide PSUR submission requirements. Additional pharmacovigilance activity: None
Serious opportunistic infections, including PML	Routine risk minimisation measures: Section 4.3, 4.4 and 4.8 of Teriflunomide Accord SmPC and corresponding sections of PIL have information on this safety concern Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Educational Materials (HCP guide and Patients card)	Routine pharmacovigilance activity: As summarized in RMP Part III Specific adverse reaction follow-up questionnaire for 'Serious opportunistic infections, including PML'. Additional pharmacovigilance activity: None
Missing information		
Long term safety in pediatric patients	Routine risk minimisation measures: Other routine risk minimisation measures include the prescription only status of the product.	Routine pharmacovigilance activity: As summarized in RMP Part III No Specific adverse reaction follow-up questionnaire for 'Long term safety'.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activity: 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of teriflunomide film-coated tablets. The reference product Aubagio 7 mg and 14 mg film-coated tablets is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis. 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, randomised, two-treatment, single-period, single oral dose, parallel study design in normal, healthy, adult, human, male subjects under fasting condition. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Fasting conditions are appropriate since SmPC of reference product Aubagio recommends dosing 'with or without food' and fasting conditions are considered the most sensitive condition to detect potential differences between formulations. Parallel study design is considered appropriate considering the very slow elimination of teriflunomide. 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 Teriflunomide Accord 14 mg film-coated tablets met the protocol-defined criteria

for bioequivalence when compared with the Aubagio 14 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72h}, 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.

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

Having considered the data submitted in the application and available on the chosen reference medicinal product, the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Additional risk minimisation measures are proposed for the following risks:

- Hepatic effects
- Hypertension
- Haematologic effects
- Infections
- Teratogenicity
- Serious opportunistic infections, including PML

The additional risk minimisation measures consist of: educational material (HCP guide and patient card).

The proposed educational materials for HCPs and patients are in line with the ones established for the reference product, which is endorsed. RMP version 1.2 is considered approvable.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Teriflunomide Accord is favourable in the following indication:

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to section 5.1 for important information on the population for which efficacy has been established).

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.
- **Additional risk minimisation measures.**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Teriflunomide Accord is marketed, at launch and after launch, all healthcare professionals who are expected to use Teriflunomide Accord are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare professionals
- Patient Education Card

The educational material for HealthCare Professionals (HCP) will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of Teriflunomide Accord detailed below including the tests and precautions needed for safe use at first prescription, and regularly during treatment as follows:
    - Risk of hepatic effects
        - Liver function tests are needed prior to the start of treatment and periodically during treatment
        - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them
    - Potential risk of teratogenicity
        - To remind women of child-bearing potential (WOCP) including adolescents/their parents caregivers that Teriflunomide Accord is contraindicated in pregnant women and in WOCP not using an effective contraception during and after treatment.
        - To assess regularly the potential for pregnancy in female patients including patients below 18 years old.
        - To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under Teriflunomide Accord treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the fetus.
        - To check pregnancy status before starting treatment
        - To educate female patients of child-bearing potential on the need for effective contraception during and after treatment with teriflunomide
        - To remind patients to inform their doctor immediately if they stop contraception, or prior

to changing contraceptive measures

- If female patients become pregnant despite using contraceptive measures, they should stop Teriflunomide Accord and contact their doctor immediately who should:
    - Consider and discuss with the patient the accelerated elimination procedure,
    - Encourage them to enrol in a pregnancy registry (in countries where a pregnancy registry is on-going),
    - Contact the National Registry Coordinator in the respective country who manages the enrolment of patient in the pregnancy registry (in countries where a pregnancy registry is on-going).

- Risk of hypertension
    - To check for a history of hypertension and that blood pressure should be appropriately managed during treatment
    - The need for blood pressure checks before treatment and periodically during treatment,
- Risk of haematologic effects
    - To discuss the risk of decreased blood cell counts (affecting mainly white blood cells) and the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms.
- Risk of infections/serious infections
    - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system. If serious infection occurs, consider the accelerated elimination procedure.

2. A reminder to provide patients/legal representative with a Patient Education Card, including filling-in their contact details, and to provide replacement Patient Education Cards as necessary;
3. A reminder to discuss the Patient Education Card content with the patient/legal representative regularly at each consultation at least annually during treatment;
4. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card;
5. Information on the optional service of a periodic reminder to patients on the MS One to One website about the continued need for effective contraception during treatment; At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.

The educational card for the patients is aligned with labelling information and includes the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a medicine which:
    - Should not be used in pregnant women
    - Requires concomitant use of effective contraception in women of child-bearing potential
    - Requires a pregnancy status check before treatment
    - Affects liver function

- Affects blood cell counts and the immune system

2. Information to educate the patient about important side effects:

- To pay attention to certain signs and symptoms which might indicate liver disease, or infection, and if any of these occur, to contact their doctor/HCP promptly
- To remind female patients to tell their doctor if breast-feeding
- A reminder for women of child-bearing potential including girls and their parents/ caregivers
    - to use effective contraception during and after treatment with teriflunomide
    - that your doctor will provide counselling on the potential risks to the fetus and on the need for effective contraception.
    - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately.
- A reminder for parents / caregivers or girls
    - to contact your doctor when the girl experiences menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception
- If women of child-bearing potential become pregnant:
    - To remind both patients and HCPs about the accelerated elimination procedure
    - To remind both patients and HCP about the Pregnancy Registry (in countries where pregnancy registry is on-going)
- To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved.)
- To record the first date of prescription and the contact details of their prescriber

3. To encourage the patients to read the PIL thoroughly

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

Not applicable.