15 September 2022
EMA/CHMP/792181/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Teriflunomide Mylan

International non-proprietary name: teriflunomide

Procedure No. EMEA/H/C/005962/0000

Note

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

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List of abbreviations

ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CoA	Certificate of Analysis
CQA	Critical Quality Attribute
FRCs	Functionality related characteristics
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IR	Infrared
LDPE	Low Density Polyethylene
MO	Major objection
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OPA	oriented polyamide
PDE	Permitted Daily Exposure
PP	Polypropylene
PVC	Polyvinyl chloride
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
tmax	Time to achieve Cmax
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet

XRPD	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Pharmaceuticals Limited submitted on 10 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Teriflunomide Mylan 14 mg film-coated tablets, 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 Mylan is indicated for the treatment of adult patients 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: Aubagio

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 14mg film-coated tablets
- Marketing authorisation holder: sanofi-aventis groupe
- Date of authorisation: 26-08-2013
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: 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: Alar Irs

The application was received by the EMA on	10 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 December 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2022
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	30 May 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	12 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 Mylan on	15 September 2022

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation of Teriflunomide Mylan 14 mg film-coated tablets is submitted under Article 10(1) (generic of a reference medicinal product) of Directive 2001/83/EC as amended. Bioequivalence is claimed to the reference product Aubagio 14 mg film-coated tablets marketed by Sanofi Aventis Groupe, France, authorised in the EU since 26/08/2013 through centralised procedure (EU/1/13/838).

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the fourth mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the *de novo* pyrimidine synthesis. As a consequence, teriflunomide blocks the activation and proliferation of rapidly dividing cells including activated lymphocytes which depend on *de novo* synthesis of pyrimidine to expand. Slowly dividing or resting cells which rely on the salvage pathway for pyrimidine synthesis are claimed to be unaffected by teriflunomide. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but likely includes the reduction of activated lymphocytes available to migrate into the central nervous system.

Teriflunomide is the active metabolite of immunosuppressant leflunomide indicated for rheumatoid arthritis and for psoriatic arthritis. *In vivo*, leflunomide is rapidly and almost completely metabolised to teriflunomide which is active *in vitro* and is presumed to be responsible for the therapeutic effect of leflunomide. In studies, teriflunomide has shown to reduce relapses and delay the progression of disability in patients with relapsing remitting MS.

Regarding its safety, side effects were similar to the immunosuppressant leflunomide, as leflunomide is converted into teriflunomide in the body. The most common side effects with teriflunomide (which may affect more than 1 in 10 people) are headache, diarrhoea, increased liver enzymes, nausea, and alopecia. In general, headache, diarrhoea, nausea and alopecia are mild to moderate, resolve with time and do not usually lead to treatment being stopped.

According to the reference product, the treatment with teriflunomide should be restricted to patients with:

- severe liver disease;
- severe immunodeficiency states, such as acquired immune deficiency syndrome;
- poor bone marrow function or low blood cell counts;
- severe active infections;
- severe kidney disease that requires dialysis;
- severe hypoproteinaemia.

Teriflunomide must not be used in pregnant women or during breast-feeding. Women who can become pregnant must not take Teriflunomide without using reliable contraceptive measures.

Additional risk minimisation activities have been established for patients using teriflunomide:

- Educational material for Healthcare professionals
- Educational card for patients

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

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Tablet core: lactose monohydrate, maize starch, microcrystalline cellulose (E460i), sodium starch glycolate (Type A), hydroxypropylcellulose (E463), magnesium stearate (E470b), colloidal anhydrous silica.

Tablet coating: hypromellose (E464), titanium dioxide (E171), macrogol 6000 (E1521), talc (E553b), indigo carmine aluminium lake (E132).

The product is available in OPA/Aluminium/PVC-Aluminium blister packs of 28 or 84 tablets and perforated unit dose blisters as well as in high density polyethylene (HDPE) bottles with polypropylene (PP) screw closure in packs of 84 or 98 tablets.

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 corresponds to the molecular formula $C_{12}H_9F_3N_2O_2$. It has a relative molecular mass of 270.2 g/mol and the following structure:

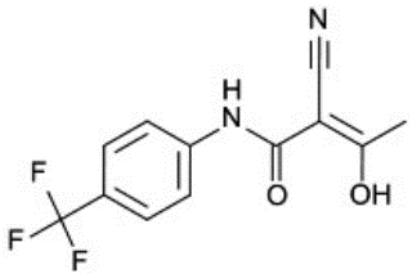

Figure 1: Active substance structure

There is a monograph of teriflunomide in the European Pharmacopoeia (07/2021:3036).

Sufficient information on elucidation of structure and other characteristics has been provided. The chemical structure of teriflunomide has been elucidated by UV, IR, mass spectroscopic analysis, ^{1}H-NMR

and ^{13}C NMR and elemental analysis with representative spectra provided. The representative spectra have been provided.

The active substance is a white or almost white powder, practically insoluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane and is non-hygroscopic in nature.

Teriflunomide has no chiral centre. Due to presence of double bond E/Z isomerism is possible. The active substance is Z isomer. Presence of desired single isomer has been confirmed based on the spectral and analytical data.

Polymorphism control is not foreseen by the Ph. Eur. monograph but the two-theta values of the Form obtained using the active substance manufacturer process are routinely tested by XRPD test at release. The polymorphic form remains unchanged following storage at long term and accelerated conditions (supported by stability data).

The material can be micronised by the active substance manufacturer as per the particle size requirement of the finished product manufacturer. The process has been described in sufficient detail.

The active substance documentation is presented in the form of an Active Substance Master File (ASMF).

2.2.2.2. Manufacture, characterisation and process controls

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

The manufacturing process of teriflunomide followed at the active substance manufacturing site is a two-step process using commercially available well defined starting materials with acceptable specifications.

The proposed starting materials are commercially available, commodities in a pre-existing non-pharmaceutical market, in line with requirements of ICH Q11.

There are no alternative steps, reprocessing carried out and recovered solvents used in the manufacturing process of the active substance.

In-process controls have been adequately described. Critical process parameters have been identified and justified.

There are several intermediates isolated in the process. Issues raised in connection with the proposed control strategy have been resolved. Although the process of teriflunomide does not involve aseptic processing or sterilisation, process validation data is provided.

The manufacturing process development has been described and although is considered rather generic, it is considered sufficient.

Discussion on actual and potential impurities that are likely to arise during the synthesis has been provided and the mechanisms utilized for their control are presented. The presented discussion on genotoxic impurities has been updated to address a Major Objection (MO) raised by the CHMP. The ICH classification (class 1 – class 5) of all impurities with an alerting structure for genotoxicity according to ICH guideline M7 (R1) has been provided. The fate and carry-over of pGTI has been addressed and control strategy in compliance with ICH M7 demonstrated.

Solvents used in the process are tested in the final active substance at ICH Q3C limits.

An elemental impurities risk assessment in line with ICH Q3D has been provided. Evaluation was performed according to ICH Q3D Option 1. No risks were identified. Screening of elemental impurities by validated ICP-MS was performed. Further controls in the active substance are deemed unnecessary.

No inorganic metal catalysts are used in the manufacture of teriflunomide. Inorganic impurities are controlled by sulphated ash at NMT 0.1%.

A risk assessment on nitrosamines has been provided by the active substance manufacturer. It is confirmed that there is no risk relating to nitrosamine impurities.

The active substance is packaged in double polyethylene bag (inner translucent HM/HDPE bag and outer black polyethylene bag) tied by plastic seals and kept in fibre board drum and HM/HDPE drum. The primary packaging material complies with EC 10/2011 as amended.

2.2.2.3. Specifications

The active substance specification includes tests for description (Ph. Eur.), solubility (in-house), identification (IR), water content (KF), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GCHS), and polymorphic form (XRPD). The specifications have been uniquely identified by number and date and chemical names of the impurities included in the specifications as a footnote.

Parameters included in the specification cover critical aspects for ensuring the quality of the active substance and the proposed specifications are in line with the Ph. Eur. monograph for teriflunomide. In addition, the active substance manufacturer controls residual solvents and polymorphic form of the active substance. Microbiological purity is not controlled at release but the parameter was tested during the stability study at accelerated and long-term conditions. Omission of the test by the finished product manufacturer is considered acceptable. Since the active substance is not sterile and not intended for use in a sterile medicinal product, it is accepted to omit the control of microbiological purity.

The proposed acceptance criteria are in accordance with relevant guidelines and are justified.

Several impurities of the process are controlled at intermediate level and the proposed control strategy is considered approvable.

Several impurities of the process are controlled at intermediate level. The limits of some of these impurities were tightened during the review as requested by the CHMP.

The control strategy for residual solvents is considered acceptable, these are limited according to ICH Q3C requirements.

The analytical methods used have been adequately described. Validations of in-house methods have been performed in accordance with ICH Q2 (R1). For related substances/assay the active substance manufacturer uses in-house analytical procedures which are not in line with the permitted adjustments of monograph 2.2.46. Quality equivalence of the in-house and Ph. Eur. methods has been demonstrated.

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

Batch analysis data (3 batches,) are provided. The results are within the proposed specifications.

2.2.2.4. Stability

Stability data from 6 bathes, manufactured by the active substance manufacturer, stored for up to 24 and 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 active substance was stored in the intended commercial package.

The following parameters were tested*:* appearance, ID by IR and HPLC, water, related substances, assay by HPLC and in addition: XRPD and microbiological purity.

The samples have been tested as per analytical methods used for release. The quality specifications have been updated several times, namely limits for related substances have been tightened since manufacturing of initial batches and test for water content included as per Ph. Eur. monograph for teriflunomide. Based on the stability data provided, each parameter remained within specifications at all time points and under both storage conditions as per currently valid tighter limits (no upwards trends in impurities seen) as well as the polymorphic form stayed unchanged.

The stability indicating nature of the in-house HPLC methods are demonstrated by means of forced degradation study. The sample of teriflunomide was exposed to thermal degradation, photostability, water, acid, base and oxidation. Degradation observed in water, acidic and oxidative degradation conditions. The photostability testing confirmed that the active substance is not sensitive to light.

The active substance manufacturer proposes a re-test period of 60 months with a requirement to store the active substance in well-closed containers and packed in commercial package. There are no special storage conditions concerning the temperature as the active substance shows good stability also at accelerated conditions. The proposed re-test period is accepted.

Additional data provided by applicant only

The finished product manufacturer has provided additional stability data on section S.4 and S.5.

The specification of teriflunomide active substance followed at the finished product manufacturing site is generally in line with the active substance specification followed by the active substance manufacturer. In addition, particle size distribution was tested based on the particle size results observed in the active substance lot used in the manufacturing of the finished product batch used for bio-equivalence study.The analytical procedures for assay/impurities used by the finished product manufacturer to test teriflunomide active substance are identical to those being followed by active substance manufacturer.

Batch analysis data on two active batches tested by the finished product manufacturer according to the proposed specifications have been presented. The results are within the applied specifications.

The quality of the reference standards used by the finished product manufacturer are considered suitable for their intended use. Further information is deemed unnecessary.

The finished product manufacturer applies a re-test period of 12 months and storage condition: "Store in well-closed containers".

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product consists of 14 mg immediate release film-coated tablets. The tablets are pale blue to pastel blue film-coated, round shaped, biconvex with a diameter of approximately 7.6 mm, debossed with "T" on one side and '1' on other side.

Teriflunomide film-coated tablets are manufactured as single strength of 14 mg, not intended for splitting in halves.

Teriflunomide Mylan 14 mg film-coated tablets have the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as the reference medicinal product. The excipients for pharmaceutical development of the finished product were selected based on the excipients

used in reference product, drug-excipient compatibility study, literature search and prior experience of product development.

The list of excipients is included in section 6.1 of the SmPC. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. All compendial excipients – lactose monohydrate, maize starch, sodium starch glycolate (Type A), hydroxypropylcellulose, cellulose, microcrystalline, silica, colloidal anhydrous, magnesium stearate and water, purified - are tested according to the corresponding Ph. Eur. monographs and meet the specified requirements. The mixture Opadry Blue is used as a coating excipient. The compatibility study data showed that Teriflunomide is compatible with all the excipients used. The choice of excipients is justified and their functions explained.

The applicant has performed an assessment for the functionality related characteristics (FRCs) tests for excipients used in the formulation. Specifications for lactose monohydrate, microcrystalline cellulose and magnesium stearate are update to include particle size test and specifications for colloidal anhydrous silica to include surface area test.

Colloidal Silicon dioxide is used in the intended commercial formulation in addition to the excipients in the reference medicinal product core tablet. The use of this excipient is justified based on manufacturability considerations. In drug-excipient compatibility study the degradation products for teriflunomide + colloidal silicon dioxide mixture remain low. Hence, the formulation difference is considered not to be significant and the composition of the intended commercial formulation is acceptable. Teriflunomide 14 mg film-coated tablets are packaged in two different marketing packs i.e. either:

- cold form blister pack comprising of cold forming material (OPA/Aluminium/PVC) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Blister strips will be placed in an outer cardboard carton;

or in:

- high density polyethylene (HDPE) bottle pack comprising of HDPE bottle with white opaque polypropylene (PP) screw closure with aluminium induction sealing liner wad, either placed in an outer cardboard carton or provided without a carton.

The initially intended bulk holding time could not be accepted and consequently the information on bulk hold time has been removed from the dossier as well as information on bulk packaging material.The finished product has been developed to be a generic equivalent to the reference medicinal product Aubagio. Consequently, the objective was to prepare a film-coated tablet being essentially similar to the reference medicinal product.

The finished product development was performed through a systematic evaluation using risk assessment methodologies. A Quality target product profile (QTPP) and critical quality attributes (CQAs) are used for finished product development.

The QTPP for teriflunomide tablets 14 mg are defined. The QTPP was to develop an oral immediate release tablet containing 14 mg of teriflunomide bioequivalent to Aubagio 14 mg, with at least 24 months shelf life at room temperature in the proposed container closure system.

The following finished product CQAs were identified: identification, assay, content uniformity, related substances, dissolution, water content and microbiological test. Content uniformity, related substances, and dissolution were further identified for explicit tracking in risk assessment given their greatest potential to be altered by process variables or formulation variables. A summary of the knowledge gained throughout development experiments to production scale associated with processing parameters and their impact on critical quality attributes of film-coated tablets has been provided. The process

compensates for the variability in the material attributes. A control strategy of the material attributes and process parameters are proposed which includes in-process controls and finished product specifications.

A summary of formulations used during development is provided. Changes between the proposed commercial formulation and those used in formulation studies batches are described and the rationale for the changes provided. The chosen formulation adequately accommodates the active substance's physicochemical properties i.e. solubility, route of administration.

No polymorphic change has been detected during finished product manufacturing and stability testing. Polymorphic identification test by PXRD is included in finished product manufacturer`s active substance specification and only one active substance crystalline polymorph form has been identified in the active substance studies. It is acceptable that crystalline form is not controlled routinely during finished product manufacturing.

Formulation trials were executed employing different levels of each process variable and evaluated for the affected CQAs. The final ranges for process parameters were determined based on the results of these studies.–From the presented data there are no differences in the manufacturing processes of the commercial product and clinical trial material.

Teriflunomide film-coated tablets are manufactured by standard processes of dry mixing, wet granulation, drying, milling, blending, compression and film-coating. Wet granulation process was chosen due to extremely poor flow nature of the active substance. A similar risk assessment as for formulation was conducted to evaluate the risk associated with various process variables.

According to the biopharmaceutical classification system (BCS), teriflunomide is BCS class II compound, with good permeability, but poor solubility. Solubility of teriflunomide varies across the physiological pH range with low solubility acidic and neutral media (practically insoluble in water). Solubility of teriflunomide increases at higher pH. This is taken into account in the evaluation of suitability of the *in vitro* dissolution method and of the comparative dissolution profiles submitted for investigation of similarity. The applicant has compared three production scale batches of the applied product with the reference product Aubagio batch used in BE study in the media selected for dissolution method.

In addition, the batch of the applied product used in BE study has been evaluated for similarity with reference product Aubagio BE batch in multimedia.

All the evaluated batches at all three conditions are similar.

The provided dissolution profiles comparison data is considered sufficient. Based on the dissolution method development studies, the dissolution method for Quality Control was. Considering the physico-chemical characteristics of the active substance and based on reflection paper EMA/CHMP/CVMP/QWP/336031/2017 the choice of the method, including rotation speed, is justified.

The discriminative power of the dissolution method has been adequately demonstrated on two different "bad batches" (changed formulation with increased concentration of one of the excipients; manipulation in manufacturing). The discriminatory nature of the applied method is demonstrated at relevant time points The acceptance criterion was initially applied by the applicant was not considered acceptable given the results from the. biobatch and the acceptance criterion in Ph. Eur. Teriflunomide tablets monograph, in place since 1 April 2022. Consequently, the finished product specification limit for dissolution was tightened during the MAA review. Additional data is also presented to prove the revised dissolution limit is met in batch analysis and in long term stability studies as well as in accelerated stability studies.

The selected container closer systems are common for this dosage form. The product will be marketed in cold form blisters (OPA/Aluminium/PVC-Aluminium) that is similar to reference medicinal product packaging material (Al/Al blisters) packages of N28 and N84 and perforated unit dose blisters of N28 x

1, N84 x1 and N98 x 1. Additionally, HDPE bottle with polypropylene (PP) screw closure of N84 and N98 is also proposed for marketing. The HDPE bottle pack is not authorised for the reference medicinal product. The materials comply 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

Teriflunomide film-coated tablets manufacturing process consists of 10 main steps: dispensing of raw materials, dry mixing, wet granulation, drying, milling, blending, compression, film-coating, inspection and packaging. The process is considered to be a standard manufacturing process.

The description of manufacturing process is in line with manufacturing process development provided. The provided data are considered sufficient for manufacturing procedures of conventional solid oral dosage formulation. The commercial batch scale range has been defined.

Information about the used equipment, the applied in-process control tests and the process parameters are complemented in the manufacturing process narrative to be in line with process validation.

Process control of critical steps (drying, blending, compression, film coating and packaging) are provided together with test methods and acceptance criteria and are considered acceptable to reduce the risks identified during formulation and process development. All relevant in-process controls and process parameters are in line with the acceptable process ranges established by manufacturing process validation. The in-process control limit for water has been tightened to be in line with the tightened water content limit for finished product at release.

Major steps of the manufacturing process have been validated by a number of studies on three 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.

In the manufacturing process validation study the packaging process is mentioned only in the process flow-chart and no other information that the tablets of validation batches were finally packed in the packages proposed for marketing (HDPE bottle and blister) is available. As the packaging process is one step in the finished product manufacturing process, the applicant was requested to clarify this aspect. He has confirmed that he will perform process validation studies on the first three maximum production scale batch, in line with the process validation scheme presented. Since the manufacturing process is a standard process, this is considered sufficient, especially as full scale process validation data, except for packaging step, has been provided already for three production scale batches of the lowest production batch size. A bulk holding time was proposed by the applicant. To accept the proposed bulk product hold time and storage conditions, additional stability study results with a minimum of 1 additional batch are required to demonstrate that the product in bulk packaging meets the updated finished product shelf-life specification limits in section 3.2.P.5.1 during the proposed hold time period under the proposed storage conditions detailed in section 3.2.P.3.3, when tested according to the methods described in updated section 3.2.P.5.2. Considering that the applicant has stated that this data cannot be provided, no storage time and conditions can be confirmed for bulk product and hence the proposed bulk holding time cannot be accepted. As such, this information has been removed from the respective sections of the dossier.

The expiration period of a batch is calculated in accordance with the EU guideline Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).

2.2.3.3. Product specifications

The specification for batch release and shelf-life includes tests for description and dimensions (visual), identification (HPLC, UV), dissolution (UV), uniformity of dosage units (content uniformity) (in-house as per Ph. Eur. General Chapter 2.9.40), assay (HPLC), related substances (HPLC), water content (KF), microbial limits and colorants ID (visual, UV). The proposed specifications include all relevant parameters to the dosage form. Hardness, average weight and friability are tested as IPC during compression stage, this is considered sufficient. The specifications have been identified by a version number and date of approval.

During the MAA assessment, a MO was raised on the proposed related substances method, which was not suitable to detect one of the specified impurities (with mutagenic potential) at sufficient low level, and the proposed specification limits for this impurity. As a result, the originally proposed 'in-house' analytical methods for related substances, assay and identification were updated with methods which are in line with the Ph. Eur. monograph for teriflunomide tablets. The revised applied limits for the specified impurities A and B and for any other impurities are in line with Ph. Eur. monograph for teriflunomide tablets. Batch and long term stability data obtained with this newly proposed method demonstrate that the actual control criteria of this impurity in the finished product is in compliance with the Ph. Eur. With this newly proposed method, additional comparison of impurity profiles of reference and test product was presented. The obtained data demonstrates that the reference and test product are comparable in terms of impurity profile. The MO raised in this aspect during the review was considered resolved.

As mentioned above, the dissolution specification limit in the finished product release and shelf life was tightened during the MAA review in line with the biobatch and recommendations of the reflection paper EMA/CHMP/CVMP/QWP/336031/2017. As discussed above, the discriminatory nature of the applied dissolution method is demonstrated for the selected time-point, both at release, and long term and accelerated stability conditions. The control limits for water content were also tightened in the release and shelf life specification upon request from the CHMP. The shelf-life limit has been further tightened to be in agreement with stability results as well as with the theoretical water content in the tablets to guarantee the quality of the finished product during shelf life.

To assure that the results of dissolution, impurities, including the specified, water content and dissolution during stability are within the updated acceptance criteria (in line with the requirements of the Ph. Eur. and relevant guidance documents) throughout the proposed shelf-life, additional long term stability data was provided during the review using newly applied analytical methods. All the results from the stability studies presented meet the updated shelf-life specifications criteria. Also, photostability data using newly proposed impurities analytical method was presented with complying results. The relevant stability data from accelerated studies is not available, therefore the CHMP recommended to present this data (REC1).

Analytical procedures have been described in sufficient detail and are adequate to control the finished product on a routine basis.

In the original submission only batch analysis data of three commercial scale batches packed in bulk packaging were presented. During the procedure also CoAs with the results from the product packed in the commercial packaging and tested as per updated analysis method were provided, showing compliance to the revised release specifications, including updated methods for impurities, dissolution and water content. The revised analytical methods for assay, related substances and identification testing according to Ph. Eur. Monograph for teriflunomide tablets (04/2022:3037) are used for testing.

Overall, the revised specification limits and test methods confirm consistency and quality of the manufacturing process.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach according to the 'ICH guideline Q3D on elemental impurities. Batch analysis data on three finished product batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A risk evaluation concerning the 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Information regarding the reference standards used for assay and impurities testing has been presented. Considering that quantitative analytical methods according to Ph. Eur. monograph for teriflunomide tablets are applied for assay, impurities and identification analytical testing now, Ph. Eur. Reference standards for teriflunomide assay, teriflunomide identity, leflunomide impurity A and teriflunomide impurity B available from EDQM are to be used for commercial batches testing.

The selected container closer systems (HDPE bottle and blister packs) are common for the applied dosage form. The blister packaging (made of aluminium foil and a foil consisting of polyvinylchloride, aluminium and polyamide) is similar to the one used for the reference medicinal product (aluminium/aluminium blister). Specifications, method of analysis and CoA of all primary packaging materials as well as declarations of compliance, when relevant, with the EU Directive 10/2011 and amendments are provided. The materials comply with Ph. Eur. and EC requirements. Additionally, test for dimensions has been included in HDPE container specification and drawings of the container closure systems presented.

Quality data regarding the bulk packaging has been provided and is acceptable. However, as indicated above, considering that the relevant bulk hold time studies are not available, no bulk hold time can be accepted for the product and as such the applicant has updated the respective sections of the Module 3, removing bulk hold time and packaging information.

2.2.3.4. Stability of the product

In the original submission, the applicant proposed a 24-month shelf life for the finished product in the container proposed for marketing, with no special storage conditions. No in-use shelf life is applied for the HDPE bottles.

The initially proposed storage condition: "This medicinal product does not require any special storage conditions" have been updated during the review to "Store below 25°C".

For the bulk product a hold time was requested. Stability data from three production scale batches of the finished product packed in the primary packaging materials proposed for marketing (blister and bottle packs) and in bulk pack was provided.

For the finished product packed in bulk packaging 12-months stability data under long term conditions (i.e. 25 ºC / 60% RH) and 6-months data under accelerated conditions were provided. The batches were only tested as per initially proposed specification methods and limits. However, to accept the bulk hold time, it should be demonstrated that product in bulk packaging meets the updated finished product shelf-

life specification limits during the proposed hold time period of 12-months under the proposed storage conditions, when tested according to the methods described in updated analytical methods section. As discussed above, the proposed bulk holding information has been removed from the dossier.

24-months stability can be confirmed for product in marketing pack when stored under 25 degrees.

To support the proposed shelf-life, 24 months data on batches stored under long term conditions (i.e. 25°C / 60% RH) packed in final packaging material proposed for marketing, tested as per newly proposed analysis methods was provided during the review. 6 months stability data under accelerated conditions (i.e. 40°C / 75% RH) on finished product packed in marketing packaging materials tested as per initially applied analysis methods was provided. Although the applicant provided information on dissolution results at accelerated conditions for the updated acceptance criteria, that are meeting the revised specification, no stability data at accelerated conditions tested as per revised assay and related substances analysis methods is available.

Samples were tested for appearance, assay by HPLC, related substances (degradants) by HPLC, dissolution by UV, water by Karl-Fisher and microbial quality (at the initial time point, at the 6-month time point and annually following long-term conditions as well as after 6 months at accelerated storage condition).

The in-use stability data and photostability data as per initially and also newly applied analysis methods has also been provided. Stability studies outside the primary container (open pot) performed as per initially applied analysis methods are submitted.

All the stability studies results in the proposed marketing packs tested at long term conditions using the newly proposed analytical methods are in accordance with the newly applied specification limits. The results in photostability data and in in-use stability data demonstrate also compliance with shelf-life specification. No in-use shelf-life is applied in the product information for HDPE bottles. This is acceptable and endorsed as in-use stability is not critical for the applied formulation of solid oral dosage form.

Consequently, the proposed shelf-life of 24 months can be accepted. However, as there is lack in results obtained under accelerated conditions the initially applied storage conditions "This medicinal product does not require any special storage conditions" as stated in the SmPC (section 6.3) cannot be confirmed yet. The currently available data at accelerated conditions obtained with initially applied analysis method for related substances (not capable to detect a specified impurity at sufficiently low level) cannot be considered adequate and hence only storage below 25 degrees protected from light can be accepted now. The storage conditions defined in the SmPC (section 6.3) and section 3.2.P.8.1 have been revised accordingly.

Since the applied special storage condition "Store below 25°C" pose unnecessary burden for the users an accelerated stability study, as well as intermediate stability study, using the revised analytical methods for assay and related substances should be initiated to evaluate whether all the parameters meet the acceptance criteria as established in the updated finished product shelf life specifications also under those conditions. In case the results from the accelerated and/or intermediate conditions confirm that the finished product does not need restrictions in storage condition ("Store below 25°C"), a variation application supported by relevant stability data to update storage conditions should be submitted (REC1). The corresponding post-approval stability commitment has been taken by the applicant and is presented in section 3.2.P.8.2. and 1.1.6.

Based on available stability data, the proposed shelf-life of 2 years and storage condition: 'store below 25°C' as stated in the SmPC (section 6.3) are acceptable.

2.2.3.5. Post approval change management protocols

n/a

2.2.3.6. Adventitious agents

It is confirmed that the lactose 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

The product is a generic of Aubagio. Information about the synthesis process and the control mechanisms for the active substance is provided in the form of the ASMF.

There is Ph. Eur. teriflunomide tablets monograph, in place since 1 April 2022.

All issues raised on applicant's and restricted parts of the ASMF have been sufficiently resolved.

A major objection that was raised regarding the finished product quality is resolved as well as other concerns. A post approval commitment on stability investigations has been taken by the applicant.

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

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the lack of intermediate and accelerated stability studies using the finished product specification analytical methods which were revised during the marketing authorization review to confirm whether the finished product storage condition restriction is necessary. The point is put forward and agreed as a recommendation for future quality development.

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress. the CHMP recommends the following point for investigation:

- Since the applied special storage condition "Store below 25°C" pose unnecessary burden for the users an accelerated stability study, as well as intermediate stability study, using the revised analytical methods for assay and related substances should be initiated to evaluate whether all the parameters meet the acceptance criteria as established in the updated finished product shelf life specifications also

under those conditions. In case the results from the accelerated and/or intermediate conditions confirm that the finished product does not need restrictions in storage condition ("Store below 25°C"), a variation application supported by relevant stability data to update storage conditions should be submitted. A commitment has been taken by the Applicant.

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

The Applicant has provided in the ERA report in addition to Phase I PECsw calculation based on annual consumption data (resulting in PECsw 0,002145 µg/L) also Phase I assessment based on European disease prevalence data (resulting in PECsw 0,00798 µg/L, if all cases would be theoretically treated with teriflunomide). Although prevalence is given for Europe, not by EU Member States, PECsw based on annual consumption data was given for the Member State with highest Fpen (Denmark in 2019). As approximately 9% of the theoretically eligible European patients are currently treated with teriflunomide, it is unlikely to achieve PECsw higher than 0,003 µg/L, even if the introduction of generic teriflunomide products should trigger a change of current treatment guidelines and accordingly increase in prescription in Member States with lower consumption of teriflunomide. Phase II environmental fate and effects analysis are not necessary as action limit 0,01 µg/L would be not exceeded with introduction of a new generic product

2.3.3. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is considered acceptable by CHMP since teriflunomide is a well-known active substance and bioequivalence is claimed to the reference product. The SmPC of the proposed drug product is identical to the reference product.

The applicant has provided data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected. The ERA is considered acceptable.

2.3.4. Conclusion on the non-clinical aspects

CHMP concluded that the non-clinical information submitted as part of this application supports the use of Teriflunomide Mylan 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.

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.

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

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study Protocol ID: CLCD-095-19, Mylan Protocol No: TERI-1-19134, Project ID: RP.19.0655: A randomized, balanced, two-treatment, single period, single oral dose, parallel, pivotal, bioequivalence study of Teriflunomide 14 mg film-coated tablets of Mylan Laboratories Limited, India, with AUBAGIO® (Teriflunomide) 14 mg film-coated tablets, of Sanofi-aventis groupe, France, in healthy adult male subjects, under fasting condition.

Methods

- **Study design**

Study no. TERI-1-19134 was a randomized, balanced, two-treatment, single period, single oral dose, parallel bioequivalence study in healthy, adult subjects under fasting conditions. Each subject received either a single, oral dose of 14 mg of teriflunomide test product or the reference product AUBAGIO® according to the randomization scheme.

Food and fluid intake

Subjects were confined to the clinical facility at least 11 hours prior to drug administration. After an overnight fast of at least 8 hours, subjects were administered a single 14 mg dose as a tablet of either the test or the reference product. Drug administration was assisted with 150 mL of ambient temperature water.

During confinement study hours, when fluids were not restricted, subjects were allowed water *ad libitum*, however, general water consumption was controlled. No fluid except that given with drug administration was allowed from 1 hour prior to dose administration to 1 hour following dose administration.

A standard low-fat dinner was provided on the evening prior to dosing. The subjects were in fasting condition for at least 8 hours prior to dosing and until 4 hours after dosing. On dosing day standard low-fat meals were provided during confinement to the clinic at 4.00, 8.00 and 12.00 h post-dose. On the

next days standardized meals were served at appropriate times i.e around 8 am, 12 noon, 4 pm and 8 pm. All meals during the study were free from broccoli, Brussels sprouts, char-grilled meat, pomegranate, Seville oranges, star fruit, grapefruit and grapefruit-, xanthine-, and caffeine-containing products.

Sampling schedule

22 blood samples (1 x 4 mL) were collected from each subject during each period for the assessment of teriflunomide in plasma. Blood collections were performed prior to the administration of study medication (0; pre-dose within a period of 1 hours before the dosing) and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours following study drug administration.

In order to reduce the risk of toxicity and to accelerate the elimination procedure of teriflunomide from the body, subjects were administered 8 g of cholestyramine powder three times a day for 11 days starting from Day 5 (after the 72.00 h post-dose blood sample collection) to Day 15 with 150 mL of mango juice. A total dose of 24 g/day was administered to the subjects per day. A single blood sample of 2 mL was withdrawn from each subject through direct venipuncture on Day 16 in order to estimate teriflunomide blood level concentration. Additional blood samples were collected after day 16 if the desired safer level of teriflunomide concentration was not achieved. The acceptable concentration limit of teriflunomide was < 20 ng/mL. The subjects were allowed to leave the clinical facility after the day 16 blood sample collection.

Approximately 113 mL of blood per subject was collected from each subject over the course of the study

- **Test and reference products**

Test Product: Teriflunomide film-coated tablets 14 mg by Mylan Laboratories Limited

Reference Product: AUBAGIO® 14 mg film-coated tablets by sanofi-aventis groupe, Paris, France (manufactured by Sanofi Winthrop Industrie, Tours, France);

- **Population(s) studied**

A total of 48 healthy male subjects (not Hispanic ethnicity, aged 19 – 43 years, BMI 19.00 – 30.00 kg/m^2) were included in the study. Only non-smokers were allowed in this study.

All 48 subjects completed both study phases and were included in the pharmacokinetic and statistical analysis.

Drop outs: There were no drop-outs in the study.

One subject withdrew consent after completion of all pharmacokinetic samples due to personal reasons

- **Analytical methods**

Teriflunomide concentrations in plasma samples of the study subjects were analysed using a validated LC-MS/MS method over a concentration range of 7.521 to 4998.450 ng/mL. Teriflunomide D4 was used as an internal standard.

Blood samples were collected into pre-chilled K_2EDTA tubes and centrifuged at 3500 rpm for 10 minutes at 4°C ± 2°C. After the samples had been transferred into polypropylene tubes they were stored at -70°C ± 10°C until assay. Study drug was extracted from 100 µl of plasma using protein precipitation technique. From instrumentation HPLC System from Shimadzu Prominence, Agilent 1100 series, mass spectrometer API 4000 and API 4000 QTrap, MDS Sciex from Applied Biosystems and Applied Biosystems/MDS SCIEX Analyst Version 1.4.2 and 1.6.1 for data processing were used. The bioanalyses

were carried out between Oct 22, 2020 and Dec 17, 2020. The bioanalytical report was released and signed on Feb 01, 2021.

Method validation:

The HPLC-MS/MS method was validated over a concentration range of 7.512 ng/mL to 5002.963 ng/mL of teriflunomide with LLOQ 7.512 ng/mL. The calibration standard curve was composed of 10 non-zero levels: 7.512, 15.009, 50.030, 100.059, 250.148, 500.296, 1000.593, 2001.185, 4002.370 and 5002.963 ng/mL of teriflunomide. The 6 QC sample concentrations at LOQQC 7.512 ng/mL, LQC 21.251 ng/mL, LMQC 494.209 ng/mL, MQC 996.805 ng/mL, HQC 3993.610 and DIQC 15974.441 ng/mL were used throughout the validation. The analytical recovery from plasma was 99.24% for teriflunomide and 94.88% for teriflunomide D4.

Method performance characteristics were following:

Within-run precision (%CV)	0.53% to 2.38%	LLOQC: 1.78% to 1.90%
Within-run accuracy (%Bias)	-3.56% to 5.12%	LLOQC: -5.48% to -0.97%
Between-run precision (%CV)	1.22% to 3.45%	LLOQC: 2.52%
Between-run accuracy (%Bias)	-0.91% to 3.58%	LLOQC: -2.45%
Dilution integrity accuracy 1/4 dilution (%Bias)	0.85%	
Dilution integrity precision 1/4 dilution (%CV)	3.45%	

The linear calibration curve calculated by weighted linear regression (weight = $1/x^2$) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report were provided. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

Study sample analysis:

A total of 1109 samples including 1056 study samples and 53 safety samples were received and analysed in 23 analytical runs.

Calibration curve standards:
Calibration curve ranged from 7.521 to 4988.450 ng/ml of teriflunomide. Accuracy (%Bias) and precision (CV%) were -6.31% to 3.72% and 1.42 to 2.68%, respectively. Correlation coefficients (r) were equal to or greater than 0.9950 in analytical runs. Number of successful calibration curves used with the study samples was 23.

QC samples:
The quality control (QC) concentrations were 7.521 (LOQ QC), 19.463 (LQC), 486.585 (LMQC), 1949.460 (MQC), 3898.920 (HQC) and 15595.679 (DIQC) ng/mL for study sample analysis. Between-run precision (CV%) and accuracy (%Bias) were 0.57% to 3.59% and 0.09 to 10.42 %, respectively. No QC samples were rejected during the sample analysis.

Number of failed batches: 0
Number of re-injected batches: 0
Number of re-integrated batches: 0
Number of individual samples re-injected: 1
Number of individual samples re-integrated: 0

Reanalysis of study samples: 1 (0.09% of 1056 study samples) sample was re-assayed for analytical reasons (internal standard variation).

Incurred sample reanalysis: conducted on 110 samples (10.42 % of 1056 study samples). 100% of the concentrations obtained by reanalysis were found within 20% of their mean initial value.

Long-term stability of samples: The maximum study sample storage period from first blood draw (Oct 15, 2020) to last sample analysis (Dec 17, 2020) was 64 days. The long-term stability data of teriflunomide in human plasma covers 64 days at -70 ± 10°C (Addendum II).

All concentration values below limit of quantification were set as zero for PK analysis. The same equipment was used at analysis of samples and precision and accuracy validation. The number of QC samples was adequate, i.e. at least two QC sets or at least 5% of the total number of subject samples.

- **Pharmacokinetic variables**

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

Secondary pharmacokinetic parameters: T_{max}

- **Statistical methods**

The pharmacokinetic parameters for teriflunomide were calculated from the plasma concentration vs. time profile using Phoenix® WinNonlin® Version 8.1 (Certara L.P., USA). Statistical comparison of the pharmacokinetic parameters was carried out using SAS® Version 9.4 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

PK parameters for each individual were tabulated and graphically presented. Actual time-points of the sample collection were used for the calculation of PK parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

The log-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) were analyzed using analysis of variance (ANOVA). ANOVA was performed using PROC MIXED with the main/fixed effect of formulation. Formulation effect was tested at the 0.05 level of significance. Each analysis of variance included calculation of least-square means. Ratio and 90% confidence interval (Schuirmann's two one-sided test) based on root mean square error obtained from ANOVA were calculated for C_{max} and AUC_{0-72} using log-transformed data. Inter-subject variability was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of teriflunomide.

Criteria for conclusion of bioequivalence:

The test product is considered as bioequivalent to the reference product if the 90% confidence intervals for the geometric least square mean ratios from ln-transformed parameters C_{max} and AUC_{0-72} of teriflunomide falls within the acceptance range of 80.00-125.00%.

Results

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

Pharmacokinetic parameter	**Test N=24**		**Reference N=24**	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
$AUC_{(0-72)}$ (ng*h/mL)	**105478.582** 104692.336	± 13096.1161 12.42%	**105757.457** 105015.952	± 12710.9119 12.02%
C_{max} (ng/mL)	**2363.783** 2337.259	± 369.7160 15.64%	**2400.545** 2365.415	± 414.0774 17.25%
T_{max}* (h)	1.75	0.50 - 3.50	1.38	0.50 - 4.00
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 h			
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 (%)**	**Inter-Subject CV%***
$AUC_{(0-72)}$	**99.69**	93.89 – 105.85	12.41
C_{max}	**98.81**	91.20 – 107.05	16.64
* estimated from the Residual Mean Squares			

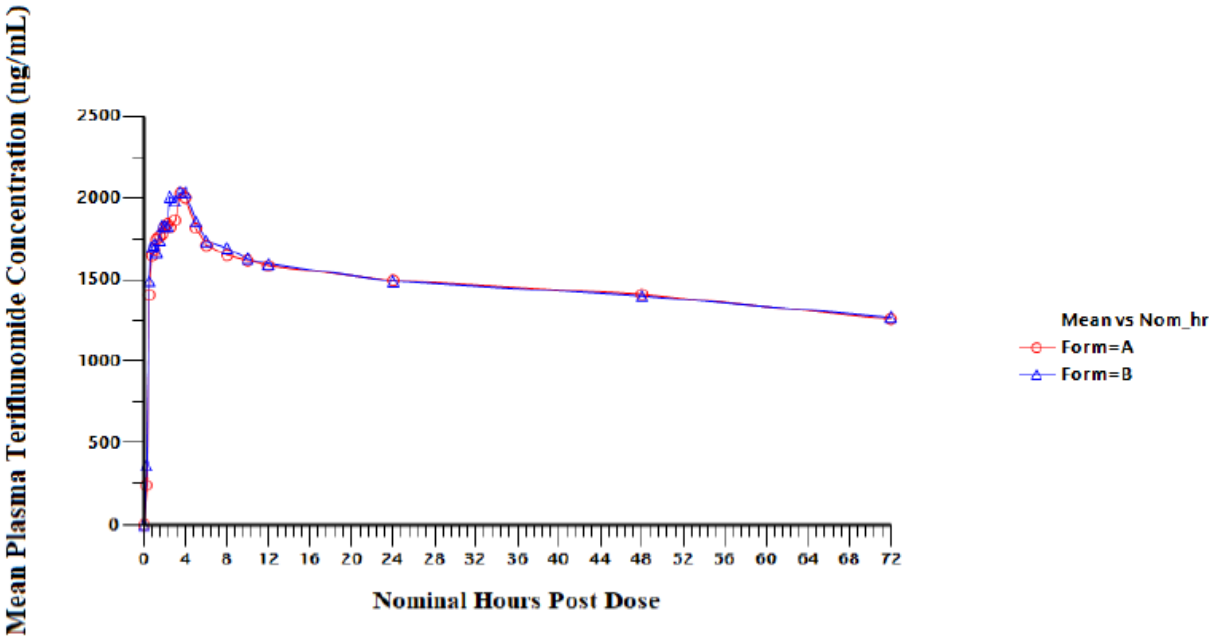

Figure 2: Mean plasma concentration vs. time curve for teriflunomide after administration of test (A) and reference (B) formulations to healthy subjects (N=24)

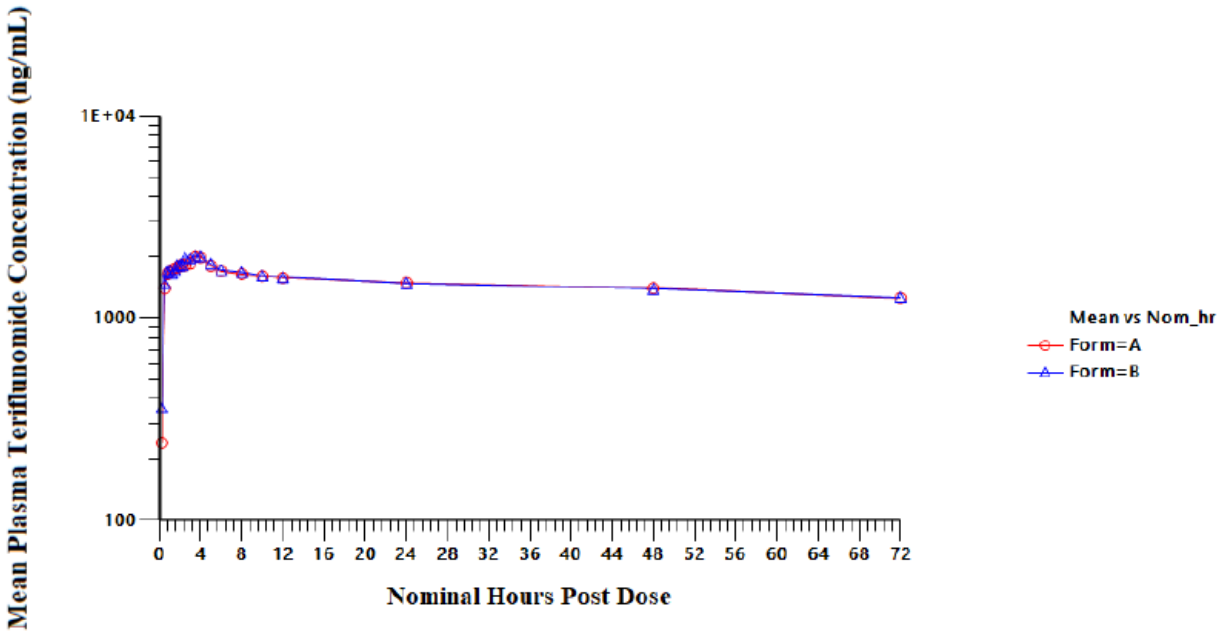

Figure 3: Semi-logarithmic plot of mean plasma concentration vs. time curve for teriflunomide after administration of test (A) and reference (B) formulations to healthy subjects (N=24)

Based on the ANOVA results, formulation effect was found to be statistically insignificant on ln-transformed scale for C_{max} and AUC_{0-72}.

- **Safety data**

A total of 11 adverse events (AEs) were reported in 10 subjects during this study. All adverse events were mild to moderate/severe in severity.

4 AEs (constipation – 2, pruritus – 1, drug eruption – 1) were reported after administration of the test product. Drug eruption was evaluated as possibly related and constipation and pruritus unlikely to be related to the drug treatment.

2 AEs (constipation – 1, gastritis – 1) were reported after administration of the reference product. Both AEs were evaluated to be unlikely related to the drug treatment.

During post-study safety assessment 5 AEs (hepatic enzyme increased – 3, blood triglycerides increased – 2). These AEs were classified as possibly related to the study drug treatment.

No serious AEs and deaths were reported during the study and in post study safety assessment.

2.4.2.2. Pharmacokinetic conclusion

Based on the presented bioequivalence study, Teriflunomide film-coated tablets 14 mg by Mylan Laboratories Limited, are considered bioequivalent with Aubagio14 mg film-coated tablets manufactured by sanofi-aventis groupe, France.

2.4.2.3. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

One single dose parallel bioequivalence study under fasting conditions was submitted to demonstrate bioequivalence with the reference product Aubagio 14 mg film-coated tablets marketed by sanofi-aventis groupe, Paris, France. 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 as most sensitive condition to detect a potential difference between formulations is justified and in accordance with the relevant guidelines. Parallel study design is considered appropriate considering the very slow elimination of teriflunomide.

Overall study design is acceptable and in line with pharmacokinetic properties of teriflunomide. The bioequivalence study was conducted under standardised conditions. The sampling period was sufficient and the sampling time schedule adequate taking into account the t_{max} of teriflunomide. The sampling schedule reached up to 72 hours and a longer period than that is not considered necessary for any immediate release formulation irrespective of half-life of the drug.

Data regarding the test and reference product were sufficient. The *in vitro* dissolution tests complimentary to the bioequivalence study comparing the in vitro dissolution similarity between the test and reference product bio-batches demonstrated similar drug release over the physiological pH range and QC media

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were

appropriate for a single dose parallel study. The 90% confidence intervals for ln-transformed pharmacokinetic variables C_{max} and AUC_{0-72} were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for teriflunomide were comparable between test and reference product. Both formulations were well tolerated in the study.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study, Teriflunomide film-coated tablets 14 mg by Mylan Laboratories Limited, is considered bioequivalent with Aubagio 14 mg film-coated tablets manufactured by sanofi-aventis groupe, France.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 3: Summary of safety concerns

Important Identified Risks	• Hepatic effects • Hypertension • Hematologic 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
Hepatic effects	Routine risk minimization measures: SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form
Hypertension	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities
Hematologic Effects	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities
Infections	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities
Acute Pancreatitis	Routine risk minimization measures: SmPC: Section 4.8 PL: Section 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Teratogenicity	Routine risk minimization measures: SmPC: Sections 4.3 and 4.6 PL: Section 2 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Continuous collection and follow-up on all cases of pregnancy with exposure to teriflunomide using specific follow-up forms; Regular submission of cumulative structured analyses of all collected pregnancy cases within PSURs
Serious opportunistic infections, including PML	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form
Long-term safety in paediatric patients	Routine risk minimization measures: Not available	Routine pharmacovigilance activities

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 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 Duloxetine Mylan 30 mg hard gastro-resistant capsules (viual presentation) and in textual content to AUBAGIO 14 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 teriflunomide film-coated tablets. The reference product Aubagio 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 a randomized, balanced, two-treatment, single period, single oral dose, parallel bioequivalence study in healthy, adult subjects under fasting conditions. 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 [applied product] met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax 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.

4. Recommendations

Outcome

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 Mylan is favourable in the following indication:

Teriflunomide Mylan 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 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 is marketed, at launch and after launch, all healthcare professionals who are expected to use teriflunomide 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 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 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 treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about

contraception and the potential risk to the foetus.

    - 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 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.
6. 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 foetus 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 foetus 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.
    - To encourage the patients to read the PIL thoroughly.