COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Teriflox 14 mg, film-coated tablets (teriflunomide)

NL License RVG: 130259

Date: 15 June 2026

This module reflects the scientific discussion for the approval of Teriflox 14 mg, film-coated tablets. The procedure was finalised on 6 November 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Teriflox 14 mg, film-coated tablets, from Maddox Pharma Swiss B.V.

The product 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 of the SmPC for important information on the population for which efficacy has been established.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, the used reference product is Aubagio 14 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/13/838/001) by Sanofi-Aventis Groupe since 26 August 2013. Since 2022 is Sanofi Winthrop Industrie the current MAH.

II. QUALITY ASPECTS

II.1 Introduction

Teriflox 14 mg, are a blue round film-coated tablets debossed with 'C14' on one side. Each tablet contains as active substance 14 mg of teriflunomide.

The excipients are:
Table core - lactose monohydrate, microcrystalline cellulose (E460), maize starch, sodium starch glycolate (type A), hydroxypropyl cellulose (E463) and magnesium stearate (E470b).
Tablet coating - hypromellose (E464), lactose monohydrate, calcium carbonate (E170), triacetin (E1518) and indigo carmine aluminium lake (E132).

The tablets are packed in aluminium/polyvinyl chloride-aluminium/oriented polyamide (Alu/PVC-Alu/OPA) blister packs.

II.2 Drug Substance

The active substance is teriflunomide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or almost white powder and is practically insoluble in water. For this product, the same polymorphic form is consistently manufactured.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the CEP, with additional requirements for particle size distribution (PDS). Batch analytical data demonstrating compliance with this specification have been submitted for three batches.

Stability of drug substance

The re-test period of the active substance is 60 months, when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Comparative dissolution at pH 1.2, 4.5 and 6.8 has been demonstrated in support to the bioequivalence study. The QC dissolution method has been sufficiently justified. The optimal composition and manufacturing process parameters have been adequately investigated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by a wet granulation process which consists of blending, granulation, lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches of the minimum batch sizes. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. and in-house (for colourant) requirements. Particle size distribution, as functionality related characteristic, is tested by the excipient providers and included in the excipient specifications. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, content uniformity, average tablet mass, assay, related substances, genotoxic impurities, dissolution and microbial limits. The release and shelf-life limits are identical. The proposed specification is acceptable. Skip testing of microbiological controls is acceptable.

The risk evaluation on the presence of nitrosamine impurities in the product has been adequately performed and no risks are identified. This justifies the absence of any further testing for nitrosamine impurity in the drug substance and drug product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for three minimum size batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for four minimum size batches stored at 40°C/75%RH (6 months), 30°C/75%RH (24 months) and 25°C/60%RH (24 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations. No changes were observed. Based on the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Teriflox 14 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. Then the

conclusion for this medicinal product was: since Teriflox 14 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Aubagio 14 mg, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Teriflunomide is a well-known active substance with established efficacy and tolerability A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Teriflox 14 mg, film-coated tablets (Maddox Pharma Swiss B.V., Iceland) was compared with the pharmacokinetic profile of the reference product Aubagio 14 mg film-coated tablets (Sanofi-Aventis Groupe, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies (Study 20-VIN-0130)

Design

A single-dose, randomised, single-period, two-treatment, parallel, oral bioequivalence study was carried out under fasted conditions in 50 healthy adult male subjects, aged 20-43 years. 50 subjects were enrolled and dosed in two groups (24 subjects in group 1 and 26 subjects in group 2). Each subject received a single dose (14 mg) of one of the two teriflunomide formulations. The tablet was orally administered with 240 mL water after a 10-hours overnight fasting.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study under fasted conditions is acceptable as the teriflunomide film-coated tablets are for oral use and can be taken with or without reference to food intake, a food interaction study is not deemed necessary. The use of a parallel design is agreed considering the slow elimination of teriflunomide. The dosing of cholestyramine after 72-hour post-dose of teriflunomide, to accelerate its elimination is agreed as this is in line with the recommendation in the SmPC of Aubagio.

The bioequivalence study is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 50 dosed subjects completed the study as per protocol and were all included in the pharmacokinetic and statistical analysis (see table 1). Two subjects withdrew their consent after the afternoon dose of cholestyramine. However, they did have complete data for the treatment with teriflunomide. A total of 7 adverse events (AEs) were observed during the conduct of study. Three subjects reported 3 AEs after administration of test product. Three subjects reported 4 AEs after the administration of reference product. Four adverse events were possible related to the drug product. All AEs were mild. No death or serious AE was reported during entire course of the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of teriflunomide 14 mg, under fasted conditions.

Treatment N=50	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	117920 ± 19259	2355 ± 488	2.00 (0.25 - 12.00)
Reference	118466 ± 16376	2387 ± 334	1.50 (0.50 – 24.50)
***Ratio (90% CI)**	99.18 (92.62 – 106.22)	97.69 (90.07 -105.95)	–

AUC_{0-t} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 72 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80 – 125%. Based on the submitted bioequivalence study

bioequivalence with respect to the rate and extent of absorption has been demonstrated for Teriflox 14 mg and the reference Aubagio.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Teriflox 14 mg . At the time of approval, the most recent version of the RMP was version 0.4 with date of final sign-off 26 October 2023.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic effects • Hypertension • Hematologic effects • Infections • Acute pancreatitis
Important potential risks	• Teratogenicity • Serious opportunistic infections, including Progressive Multifocal Leukoencephalopathy (PML)
Missing information	• Long-term safety in paediatric patients

The summary of safety concerns for Teriflox is in line with the current summary of safety concerns for the reference product Aubagio. This is endorsed.

The Routine Risk Minimisation Measures are endorsed. The proposed additional risk minimisation measures (HCP education/discussion guide and patient education card) are accepted. This is in line with what has been established for the reference product Aubagio. The MAH stated that the Prescriber Additional Risk Minimisation Measures (aRMM) materials will be distributed together with the SmPC to all physicians who are expected to prescribe or use Teriflox. The distribution path of the aRMM materials should be agreed with the National Competent Authority before launch in a separate procedure.

Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC

- Additional risk minimisation measures (including educational material)

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

The MAH shall ensure that all healthcare professionals who are expected to use Teriflox are provided with the following items:

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

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

1. HCPs should discuss with their patients the specific safety concerns of Teriflox 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 Teriflox 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 Teriflox 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 Teriflox and contact their doctor immediately who should:
    - Consider and discuss with the patient the accelerated elimination procedure,
    - Report any pregnancy cases to Maddox Pharma BV (by calling or visiting the website) irrespective of adverse outcomes observed.
- 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.

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

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 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 PL thoroughly.

Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
- Continuous collection and follow-up on cases of pregnancy with exposure to teriflunomide (either during pregnancy or in the relevant time interval before conception considering the very long half-life of teriflunomide), including reports of pregnancy exposure without outcome data or with a normal outcome; - Use of targeted follow-up questionnaires to collect data of interest about pregnancy exposure in line with the originator product; - Regular submission of structured analyses of the pregnancy cases at harmonised submission dates (3-year cycle) synchronised with Aubagio PSUR submission requirements.	Regular submissions at harmonised submission dates (3-year cycle) synchronised with Aubagio PSUR submission requirements.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aubagio. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Teriflox 14 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Aubagio 14 mg film-coated tablets. Aubagio is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Teriflox 14 mg with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 6 November 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Art61(3)	Add English translations of the PIL and labelling to the product information.	Yes	08-01-2024	Approved	N.A.
Type IA: A.1 Type IA: C.I.8.a	Change in the name and/or address of the marketing authorisation holder. Introduction of , or changes to, a summary of pharmacovigilance system for medicinal products for human use: - Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location.	Yes No	07-02-2025	Approved	N.A.
Type IA: A.5.a	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites); - Manufacturer responsible for batch release.	Yes	31-01-2025	Approved	N.A.
Type IA: A.6 Type IB: C.I.2.a.	Change in ATC Code / ATC Vet Code. Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product. - Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes Yes	24-02-2025	Approved	N.A.
Type IA: A.6	Change in ATC Code / ATC Vet Code.	Yes	29-07-2025	Approved	N.A.
Type IB: B.II.f.1.b.1	Change in the shelf-life or storage conditions of the finished product:	Yes	23-09-2025	Approved	N.A.

	- Extension of the shelf life of the finished product - As packaged for sale (supported by real time data).				
Type IA: B.III.1.a.2	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer.	No	23-01-2026	Approved	N.A.