COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Teriflunomide Glenmark 14 mg film-coated tablets (teriflunomide)

NL/H/5511/001/DC

Date: 18 September 2024

This module reflects the scientific discussion for the approval of Teriflunomide Glenmark 14 mg film-coated tablets. The procedure was finalised on 16 August 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 Member States have granted a marketing authorisation for Teriflunomide Glenmark 14 mg film-coated tablets, from Glenmark Arzneimittel GmbH.

The product is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).

A comprehensive description of the up-to-date 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 decentralised procedure, essential similarity is proven between the new product and the innovator product Aubagio 14 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/13/838) since 26 August 2013.

The concerned member states (CMS) involved in this procedure were Czechia, Norway, Poland and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Teriflunomide Glenmark is a white to off white round biconvex film coated tablet debossed with G on one side and 42 on the other side.

And contains as active substance 14 mg of teriflunomide.

The excipients are:
Tablet core: lactose monohydrate, maise starch, sodium starch glycolate (Type A), hydroxypropyl cellulose (E463), microcrystalline cellulose (E460), magnesium stearate (E470b) and colloidal anhydrous silica.

Tablet coating: hypromellose 2910 (E464), titanium dioxide (E171), macrogol (E1521) and talc (E553b).

The film-coated tablets are packed in aluminium/aluminium desiccant blister foil packs in cardboard cartons.

II.2 Drug Substance

The active substance is teriflunomide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white powder and is practically

insoluble in water. The same polymorphic form is consistently produced and controlled in the specification.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of five chemical steps and purification. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months when stored under the stated conditions.

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.

Comparative dissolution at three pHs has been successfully studied in support of bioequivalence. 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 validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. and in-house (for colorant) requirements. 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, average weight, dissolution, uniformity of dosage units, related substances, assay, water and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three full scaled batches stored at 40°C/75% RH (6 months), 30°C/65% RH (12 months) and 25°C/60% RH (24 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage condition is 'do not store above 30°C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for excipient 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 member states consider that Teriflunomide Glenmark has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- A post-approval variation will be submitted for change of the tablet colour and remove all information of excipient X.
- The working standard will be qualified against Teriflunomide Ph.Eur. Chemical Reference Substances (CRS), for future commercial batches.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Teriflunomide Glenmark is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Aubagio which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states 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 member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Teriflunomide Glenmark 14 mg film-coated tablets (Glenmark Arzneimittel GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Aubagio 14 mg film-coated tablets (Sanofi Aventis group, France).

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

Design

An open label, balanced, randomised, two-treatment, single-period, single oral dose, parallel bioequivalence study was carried out under fasted conditions in 67 healthy male subjects, aged 18-44 years. 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 an overnight fast of

at least 10 hours. There was one dosing period. As this was a study with a parallel study design, no washout period was necessary.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 18, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Teriflunomide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of teriflunomide. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions 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 67 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=67	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	109978 ± 15781	-	2457 ± 450	1.67 (0.5 – 4.0)
Reference	112856 ± 13203	-	2458 ± 336	1.5 (0.5 – 4.0)
***Ratio (90% CI)**	0.97 (0.92 – 1.03)	-	0.99 (0.93 - 1.06)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero 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 0.80 – 1.25. Based on the submitted bioequivalence study Teriflunomide Glenmark is considered bioequivalent with 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 Teriflunomide Glenmark.

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 member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

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 6 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

Teriflunomide Glenmark 14 mg film-coated tablets have a proven chemical-pharmaceutical quality and are 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Teriflunomide Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 August 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
NL/H/5511/IB/001/G	Change in immediate packaging of the finished product. Change in type of container or addition of a new container. Solid, semi-solid and non-sterile liquid pharmaceutical forms.	Yes	30-07-2024	Approved	-
NL/H/5511/001/IB/002	Changes in the composition (excipients) of the finished product. Changes in components of the flavouring or colouring system. Addition , deletion or replacement.	Yes	30-07-2024	Approved	-