COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Teriflunomide Devatis 7 mg and 14 mg, film-coated tablets (teriflunomide)

NL/H/5632/001-002/DC

Date: 22 October 2024

This module reflects the scientific discussion for the approval of Teriflunomide Devatis 7 mg and 14 mg, film-coated tablets. The procedure was finalised on 13 January 2024. 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 Devatis 7 mg and 14 mg, film-coated tablets, from Devatis 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) (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 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 7 mg and 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 state (CMS) involved in this procedure is Germany.

II. QUALITY ASPECTS

II.1 Introduction

Teriflunomide Devatis 7 mg and 14 mg are film-coated tablets. The two strengths of the film-coated tablets can be distinguished by the colours and are as follows:

Teriflunomide Devatis 7 mg
The 7 mg tablets contain as active substance 7 mg of teriflunomide and are pale green to greenish grey, biconvex, round film-coated tablets, approximately 6 mm in diameter.

Teriflunomide Devatis 14 mg
The 14 mg tablets contain as active substance 14 mg of teriflunomide and are pale blue to pastel blue biconvex, round film-coated tablets, approximately 7 mm in diameter.

The excipients are:
Tablet core: lactose monohydrate, maize starch, microcrystalline cellulose, sodium starch, glycolate (Type A), hydroxypropyl cellulose, silica, colloidal anhydrous and magnesium stearate.
Tablet coating: hypromellose, titanium dioxide (E171), glycerol triacetate, indigo carmine aluminium lake (E132) and iron oxide yellow (E172; only for 7 mg strength).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in polyamide nylon/aluminium/polyvinyl chloride-aluminium (OPA/aluminium/PVC-aluminium) blisters in cartons.

II.2 Drug Substance

The active substance is teriflunomide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Teriflunomide is a white to almost white crystalline powder and is practically insoluble in water. The same polymorphic form is consistently produced and controlled in the specification. The structure contains no asymmetric centres, therefore no enantiomers are possible. Teriflunomide is classified as BCS class II drug substance (low solubility and high permeability). It exists as a single crystal form.

Manufacturing process
The manufacturing process consists of a two-step synthesis of the intermediate, after which this intermediate is converted in one step into the final active substance. 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 batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 3 years. Based on the data submitted, a retest period could be granted of 4 years 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. The choice of excipients is justified and their functions explained. A bioequivalence (BE) study was performed with the 14 mg product strength. For the 7 mg product a biowaiver is shown. Comparative dissolution testing at three pHs has been successfully studied in support of the BE study and biowaiver.

Manufacturing process
The drug product is manufactured by a process of sifting of raw materials, dry mixing, wet granulation, pre-lubrifaction and lubrification blending, tablet compression, film coating and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for nine validation

batches (three batches of 7 mg and six batches of 14 mg) stored in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their Ph.Eur. or in-house 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, hardness, water content, assay, dissolution, uniformity of dosage units, related substances, assay and microbiological quality. 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 nine batches (three batches of 7 mg and six batches of 14 mg) stored 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 nine batches (three batches of 7 mg and six batches of 14 mg) stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable ICH 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 three years. 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 the 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 Devatis 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)

Since Teriflunomide Devatis 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 Devatis 14 mg, film-coated tablets (Devatis 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.

Biowaiver

For the 7 mg strength, a biowaiver was granted because the following requirements were met, in accordance with the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. Dissolution studies were conducted in different pH conditions (pH 1.2, pH 4.5 and pH 6.8). The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Design

A single-dose, randomised, open label, balanced, two-treatment, truncated, parallel bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 20-44 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 at least 10 hour fasting.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 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

38 subjects enrolled in the study. Two subjects were withdrawn from the study due to personal reasons. 46 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=46	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	114.3 ± 15.3	-	2490 ± 423	1.00 (0.50-24.00)
Reference	113.3 ± 17.0	-	2462 ± 409	1.67 (0.50-4.50)
***Ratio (90% CI)**	1.01 (0.94-1.09)	-	1.01 (0.93-1.10)	-

$AUC_{0-\infty}$	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 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Teriflunomide Devatis 14 mg is considered bioequivalent with Aubagio 14 mg.

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 Devatis.

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	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information, supplemented with the following additional risk minimisation measure:

- Educational materials (health care professional education/discussion guide and patient education card)

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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Lenalidomide Devatis 2.5 mg, 5 mg,7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules (NL/H/4989/001-007/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Teriflunomide Devatis 7 mg and 14 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Aubagio 7 mg and 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 Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 January 2024.

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/5632/IA/002/G	New certificate from an already approved manufacturer (x 2)	No	9 August 2024	Approved	-
NL/H/5632/001-2/IA/003	Change(s) in the Package Leaflet of human medicinal products - Implementation of wording agreed by the competent authority - Update of product information after PSUSA	Yes	10 October 2024	Approved	-