LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Teriflunomide Genepharm
(teriflunomide)

SE/H/2320/01-02/DC

This module reflects the scientific discussion for the approval of Teriflunomide Genepharm. The procedure was finalised on 2023-11-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Teriflunomide Genepharm, 7 mg, 14 mg, Film-coated tablet.

The active substance is teriflunomide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Teriflunomide Genepharm, 7 mg, 14 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and EL as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is AUBAGIO, 7 mg and 14 mg, Film-coated tablet authorised in the union since 2013, with Sanofi-Aventis groupe as marketing authorisation holder.

The reference product used in the bioequivalence study is AUBAGIO, 14 mg, Film-coated tablet from Germany with Sanofi-Aventis groupe as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of teriflunomide are well known. As teriflunomide is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Teriflunomide Genepharm is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Teriflunomide Genepharm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing the test product Teriflunomide, 14 mg, film-coated tablets, with the reference product AUBAGIO, 14 mg, film-coated tablets.

Pharmacokinetic properties of the active substance
Absorption: Maximum plasma concentrations are reached 1 to 4 hours post-dose following repeated oral administration of teriflunomide, with high bioavailability (approximately 100%).

The pharmacokinetics of teriflunomide is not affected by food, and there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of teriflunomide is linear within the dose range 7-14 mg.

Elimination: Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg.

Study 0203-21
Methods
The study was an open-label, randomized, two-treatment, single period, single dose parallel design study conducted in 101 healthy, male volunteers under fasting conditions. After an overnight fast of at least 10 hours, one tablet of 14 mg of either test or reference was administered together with 240 ml of water. Fasting continued until 4 hours after drug administration. The subjects were provided with 33 sachets of cholestyramine 4 g at the time of check-out and were instructed to consume one sachet three times daily from day 4 to 14.

Blood-samples were collected pre-dose and at 0.167, 0.333, 0.500, 0.750, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 24.000, 36.000, 48.000 and 72.000 hours after drug administration. Also, a final blood sample was collected

on day 15, after completion of the cholestyramine administration phase.

Ninety-nine subjects completed the clinical phase of the study successfully and were included in the pharmaco-kinetic analysis.

The clinical part of the study was conducted between 04 Aug 2021 and 13 Sep 2021.

Plasma concentrations of teriflunomide were determined with an LC-MS/MS method.
Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for teriflunomide, n=99.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**115113 ± 15910**	**2345 ± 326**	**1.50 (0.33 – 4.00)**
Reference	**118077 ± 18448**	**2426 ± 481**	**1.67 (0.33 – 4.50)**
***Ratio (90% CI)**	**97.7 (93.02 – 102.68)**	**97.6 (92.15 – 103.27)**	**-**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 7 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Moreover, the bioanalytical method was adequately validated.

Absence of study with the additional strength of 7 mg is acceptable, as all conditions for biowaiver of additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), are fulfilled and since the pharmacokinetics of teriflunomide is linear between 7 mg and 14 mg.

Based on the submitted bioequivalence study, the test product is considered bioequivalent with AUBAGIO.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Genepharm.

The MAH has submitted the version 0.2 RMP dated 01-03-2023 and proposed the following summary safety concerns

Safety specification

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

The safety concerns have been identified based on published list of safety concerns of the reference product AUBAGIO® available in the EMA website (RMP v 7.3)

Assessor's comment D70: The proposed RMP is not completely in line with that of the reference product. The Missing information should be specified as "long term safety in pediatric patients" in line with the RMP version 7.3 for Aubigo.
Assessor's comment D120: The submitted Risk Management Plan, version 0.2 signed 01-03-2023 is considered acceptable. **Issue resolved.**

Pharmacovigilance Plan

Assessor's comment D70: Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant. This is not endorsed.

During the plenary meeting held on 10-13 January 2022, PRAC concluded (as triggered by another decentralised marketing authorisation application for a generic teriflunomide-containing medicinal product), that in order to further characterise the potential of teriflunomide for teratogenicity:
All applicants/MAHs of generics MAA should continuously collect and follow-up on cases of pregnancy with exposure to teriflunomide (either during pregnancy or in the relevant time interval before conception, given the product's very long half-life), including reports of (pregnancy) exposure without outcome data or with a normal outcome.
Following further coordination discussions at CMDh, it is considered most appropriate for MAHs of generic teriflunomide-containing medicinal products to submit PSURs in line with the requirements for the reference product Aubagio and to include the above described reviews on pregnancy cases in the PSURs. The requirement for regular submissions of analyses of pregnancy cases should be included under "routine pharmacovigilance activities beyond adverse reactions reporting and signal detection" in the Pharmacovigilance Plan in the RMP as follows:

- Continuous collection and follow-up on cases of pregnancy with exposure to teriflunomide (either during pregnancy or in the relevant time interval before conception, given the product's very long half-life), including reports of (pregnancy) exposure without outcome data or with a normal outcome. Use of targeted questionnaires for follow-up.

- Regular submission of cumulative structured analyses of all collected pregnancy cases within PSURs, taking the following into account in order to improve the overall product comparability:
    - Overall patient exposure data for the respective product expressed as patient-years based on World Health Organization (WHO) defined daily dose of 14 mg
    - Separate analysis of prospectively and retrospectively reported pregnancy cases; provision of details about time point of exposure to teriflunomide (before/during pregnancy, taking into account the long half-life and information on accelerated elimination procedure)
    - Use of European Surveillance of Congenital Anomalies (EUROCAT) definitions of major congenital malformations, spontaneous abortions, stillbirths etc.

As a result of this the educational material for teriflunomide generics should also be amended, also in line with the PRAC advice.
An update of the key elements of educational materials is necessary in line with the PRAC advice for generic teriflunomide medicinal products. In the HCP guide, the key elements related to pregnancy while treated with teriflunomide should be as follows:

- 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,
    - Report any pregnancy case to <marketing authorisation holder> by calling <local number> or visiting <URL>, irrespective of adverse outcomes observed.

Please amend in line with this.

Risk minimisation measures

Assessor's comment D70: Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant. This is endorsed for all safety concerns except from teratogenicity. Update the Risk minimisation measures as per comments above for the Pharmacovigilance Plan.
Assessor's comment D120: Additional risk minimisation measures are proposed for teratogenicity.
Issue resolved.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 01-03-2023 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The user test was assessed and accepted at day 70.

The package leaflet 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 PlL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Teriflunomide/Genepharm, is found adequate. There are no objections to approval of Teriflunomide/Genepharm, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Teriflunomide Genepharm, 7 mg, 14 mg, Film-coated tablet was positively finalised on 2023-11-15.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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