LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Teriflunomid SUN
(teriflunomide)

SE/H/2465/01/DC

This module reflects the scientific discussion for the approval of Teriflunomid SUN. The procedure was finalised at 2023-11-16. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Teriflunomid SUN, 14 mg, Film-coated tablet.

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

II. EXECUTIVE SUMMARY

II.1 About the product

Mechanism of action
Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

ATC code: L04AA31
EURD: 12/09/2013

Claimed indication is:
for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).

In adults, the recommended dose of teriflunomide is 14 mg once daily.
In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:
- Paediatric patients with body weight >40 kg: 14 mg once daily.
- Paediatric patients with body weight ≤40 kg: 7 mg once daily.

II.2 General comments on the submitted dossier

The application for Teriflunomid SUN (former Zolsey), 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 PL, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Aubagio, 14 mg, film-coated tablet, authorised in the EU since 2013, with Sanofi Winthrop Industrie as marketing authorisation holder.

The reference product used in the bioequivalence study is Aubagio, 14 mg, film-coated tablet, from DE with Sanofi Winthrop Industrie 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.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance an acceptable statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study been provided. No issues regarding GCP have been identified. The clinical facility and bioanalytical facility were inspected by the WHO in 2017 without any critical findings. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Teriflunomid SUN (former Zolsey) 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 Teriflunomid SUN (former Zolsey) from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Teriflunomid SUN (former Zolsey) (teriflunomide) with the reference product Aubagio.

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 C20122
Methods
This was an open label, balanced, randomized, single-dose, single-period, two treatment, parallel, truncated study conducted in 40 healthy volunteers, comparing teriflunomide, 14 mg, tablet with Aubagio, 14 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. 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_{0-72} and C_{max}. The study was conducted between 3 December 2020 and 7 December 2020.

Results

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

IV. BENEFIT RISK ASSESSMENT

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Table 1. Statistical analysis of teriflunomide

Parameters (Units)	Geometric Least Square Means				90% Confidence Limits	(T/R)%	Intra Subject CV %	Power (%)
	Test product (T)	N	Reference product (R)	N	(T vs. R)			
C_{max} (ng/mL)	2325.2072	39	2311.0411	39	93.11-108.72	100.61	14.41	99.85
AUC_{0-72} (hr.ng/mL)	110715.8760	39	111951.2784	39	92.99-105.18	98.90	11.44	100.00

**calculated based on ln-transformed data*

For AUC_{0-72} 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%.

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). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Teriflunomid SUN (former Zolsey) is considered bioequivalent with Aubagio.

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

Pharmacovigilance system

Proposed MAH: Sun Pharmaceutical Industries (Europe) B.V., Terapia S.A., Ranbaxy (Poland) Sp. z o.o.
The Applicant has submitted a revised signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Teriflunomid SUN (former Zolsey).

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2023-09-21 and proposed the following summary safety concerns:

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	• **None**

PML: Progressive Multifocal Leukoencephalopathy

Assessor´s comment: The summary of safety concerns are in line with the latest version of the Risk management plan for the reference product (version 8.1, signed 2023-03-14). This is agreed.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant. Please note that the application also includes non-conditioned follow-up questionnaires for liver injury, pancreatic effects, teratogenicity, and serious opportunistic infections, including PML as routine pharmacovigilance activities, which is in line with the reference. This is endorsed.

Part V Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic effects	**Routine risk minimisation** • **SmPC: Sections 4.2, 4.3, 4.4 and 4.8** • **PIL: Sections 2 and 4** • Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU) **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire (Drug induced liver injury form) Additional pharmacovigilance activities: • None
Hypertension	**Routine risk minimisation** • **SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4** • Prescription only medicine **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None specific Additional pharmacovigilance activities: • None
Hematologic effects	**Routine risk minimisation** • **SPC section 4.3, 4.4 and 4.8** • **and Package Leaflet Section 2 and 4** • Prescription only medicine **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None specific Additional pharmacovigilance activities: • None
Infections	**Routine risk minimisation** • **SPC sections 4.3, 4.4 and 4.8** • **and Package Leaflet Section 2 and 4** • Prescription only medicine **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None specific Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• None
Acute pancreatitis	**Routine risk minimisation** • **SPC section 4.4 and 4.8** • **and Package Leaflet Section 2 and 4** • Prescription only medicine • Limited pack sizes **Additional risk minimisation measures** • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire (pancreatic disorder form) Additional pharmacovigilance activities: • None
Teratogenicity	**Routine risk minimisation** • **SPC section 4.3 and 4.6** • **and Package Leaflet Section 2** • Prescription only medicine **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire (pregnancy reporting form) Additional pharmacovigilance activities: • None
Serious opportunistic infections, including PML	**Routine risk minimisation** • **SPC section 4.3, 4.4 and 4.8** • **and Package Leaflet Section 2 and 4** • Prescription only medicine **Additional risk minimisation measures** • Educational Materials (HCP education/discussion guide and patient education card).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted questionnaire (PML form). Additional pharmacovigilance activities: • None

Assessor's comment: The suggested risk minimisations measures are in line with those of the reference product. This is endorsed. Please see secton VI.3 of this Overview report for key elements of the educational material.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2023-09-21 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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 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)**
  The educational material should contain the following key elements:

1. Physician educational material:

• The Summary of Product Characteristics

• Healthcare professional (HCP) education/discussion guide

1.1 Healthcare professional education/discussion guide:

The educational material for HCP will include the following key elements:

- Healthcare professionals 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 fetus.

    • 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.

- 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;
- A reminder to discuss the Patient Education Card content with the patient/legal representative regularly at each consultation at least annually during treatment;
- 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;
- 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;
- 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.

2. The patient information pack:

• Patient Information Leaflet (PIL)

• Patient Education Card

2.1 Patient education card:

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

- 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

- Information to educate the patient about important side effects andto 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 fetus 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 fetus and the need for contraception
- If women of child-bearing potential (WOCP) 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

Assessor's comment: The proposed key elements are in line with those of the reference product and are therefore endorsed.

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

The approved PL is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Aubagio, 14 mg film-coated tablets (EMA/529295/2013) for content and Morphine 1 mg/ml solution for infusion in pre-filled syringe (DE/H/6814/001-002/DC) for layout.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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