LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Teriflunomide Newbury
(teriflunomide)

SE/H/2709/001/DC

This module reflects the scientific discussion for the approval of Teriflunomide Newbury. The Public Assessment Report was written in October 2022 by the previous RMS Iceland after initial procedure IS/H/0476/001/DC and is attached at the end of this document. RMS transfer from Iceland to SE was completed 2024-12-19. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

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SWEDISH MEDICAL PRODUCTS AGENCY

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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Public Assessment Report

Scientific discussion

Teriflunomide Newbury
teriflunomide

IS/H/0476/001/DC

Date: 25.10.2022

This module reflects the scientific discussion for the approval of Teriflunomide Newbury. The procedure was finalised at 21.09.2022. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Teriflunomide Newbury, film-coated tablet, 14 mg, from Newbury Pharmaceuticals AB.

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 indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to insert Article 10(1) of Directive 2001/83/EC.

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.

No discussions were held with CMDh during the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Teriflunomide Newbury is an immediate release film-coated tablet. The drug product is presented as round shaped, light blue coloured film-coated tablets with a score line. The functionality of the score-line was adequately demonstrated. The film-coated tablets are packed into aluminium/aluminium blisters and placed inside a cardboard box. The excipients and container closure systems are common for this type of dosage form.

Drug composition

Tablet core
lactose monohydrate
maize starch
cellulose microcrystalline
hydroxypropyl cellulose
sodium starch glycolate

talc
calcium stearate

Tablet coating
hypromellose
titanium dioxide (E 171)
macrogol 8000
Indigo Carmine aluminium lake (E 132)

II.2 Drug Substance

Teriflunomide is an established drug substance and subject of a monograph in the Ph.Eur. (07/2021:3036). Furthermore, a monograph for the finished product Teriflunomide tablets is available in the Ph.Eur. (04/2022:3037).

Teriflunomide is a white or almost white powder, practically insoluble in water and heptane, as well as slightly soluble in anhydrous ethanol.

The active substance specification includes relevant tests and the acceptance limits have been appropriately justified. The analytical methods applied are suitably described and validated as demonstrated with compliance to the Ph.Eur. as ASMF for the active substance confirms.

Stability studies have been conducted and the data provided is sufficient to support the proposed retest period.

II.3 Medicinal Product

The development of the drug product formulation is well described. The excipients used in the product are all standard in the manufacture of (immediate release film-coated tablet) and are compliant with European Pharmacopoeia (or equivalent) requirements.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the finished products specifications are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed in the commercial packaging and data presented support the shelf life claimed in the SPC; 30 months with no special storage conditions for the finished product in Al/Al blisters.

The pharmaceutical quality of Teriflunomide Newbury has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Abridged applications avoid the need for repetitive tests on animals and humans.

III.2 Pharmacology, Pharmacokinetics and Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of teriflunomide are well known. As teriflunomide is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Since Teriflunomide Newbury 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.4 Discussion on the non-clinical aspects

Teriflunomide Newbury is a generic to Aubagio®. Abridged applications avoid the need for repetitive tests on animals and humans.

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study to confirm that the applied product is bioequivalent to the reference medicinal product.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09.

Bioequivalence studies

To support the application, the applicant has submitted as report one bioequivalence study.

Statement of GCP compliance is provided. A statement is provided to confirm that the bioequivalence study carried out outside the European Union meets the ethical requirements of the European Union Directive 2001/20/EC.

An open label, randomized, balanced, two-treatment, single-period, parallel, oral bioequivalence study of Teriflunomide 14mg Film Coated Tablet and Aubagio® 14 mg Filmtabletten in healthy, adult, human male subjects under fasting conditions.

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

Treatment	**AUC_{0-72}** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	104388.838 (±13795.314)	2221.421 (±409.723)	2.250 (0.333, 5.000)
Reference	99995.971 (±11042.885)	2139.942 (±281.371)	1.500 (0.517, 4.000)
***Ratio (90% CI)**	104.13 (98.89 - 109.65%)	102.95 (96.19 – 110.19%)	-
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached, median			

ln-transformed values

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study/ies Teriflunomide Newbury is considered bioequivalent with Aubagio®.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

IV.5 Clinical safety

No new clinical safety studies were presented and no such studies are required for this application.

IV.6 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 Newbury.

- Summary table of safety concerns as approved in RMP

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 pediatric patients

PML: Progressive Multifocal Leukoencephalopathy.

IV.7 Discussion on the clinical aspects

Teriflunomide Newbury is a generic to Aubagio®. Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study.

The application contains an adequate review of published clinical data, and the bioequivalence has been shown between Teriflunomide Newbury and Aubagio®.

Approval is recommended from the clinical point of view.

V. USER CONSULTATION

The results of the user consultation with target patient groups on the package leaflet report submitted by the applicant 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

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Teriflunomide Newbury, that is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS). It is considered positive and marketing authorisation can be recommended.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

There was no Discussion in CMDh. There are no specific obligations and follow-up measures.