LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ramiliv
(ramipril)

SE/H/2069/01-03/DC

This module reflects the scientific discussion for the approval of Ramiliv. The procedure was finalised on 2024-03-18. 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 Ramiliv, 2,5 mg, 5 mg, 10 mg, Tablet.

The active substance is ramipril. 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 Ramiliv, 2.5 mg, 5 mg, 10 mg, 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 DK as the sole concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is TRIATEC 2.5 mg, hard capsule authorised in France since 1989, with Sanofi Aventis as marketing authorisation holder.

The reference products used in the bioequivalence study is Tritace, 5 mg and 10mg, tablet, from Romania with Sanofi Aventis S.p.A. as marketing authorisation holder.

European Reference Product (ERP)
For two of the strengths of this application a European Reference Product is used in CMS DK: SE/H/2069/01/DC: TRIATEC, 2.5 mg tablet, authorised in Sweden since 1991, with Sanofi AB as marketing authorisation holder.
SE/H/2069/03/DC: TRIATEC, 10 mg tablet, authorised in Sweden since 2001, with Sanofi AB as marketing authorisation holder.

The justification to use this product is based on RMS's own files.

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 ramipril are well known. As ramipril 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 Ramiliv 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 Ramipril from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing the sponsor´s ramipril tablets with the reference product Tritace tablets.

Pharmacokinetic properties of the active substance
Absorption: Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations (Cmax) of ramipril are reached within one hour. Ramipril is rapidly and almost completely metabolised, e.g. to the sole active metabolite ramiprilat. Cmax for ramiprilat is reached within 2-4 hours after oral intake of ramipril. The pharmacokinetics of ramipril are not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: After oral administration of the doses 2.5 mg and 5 mg ramipril, respectively, the bioavailability of the active metabolite ramiprilat is 45%. This indicates linear pharmacokinetics of ramipril in the dose interval 2.5 - 5 mg ramipril.

Elimination: Excretion of the metabolites is primarily renal. After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentration was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

Study “RAMIAIS 04/2012” – 10 mg tablet
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing ramipril, 10 mg, tablet with TRITACE, 10 mg, tablet under fasting conditions. Blood samples for

concentration analysis were collected pre-dose and up to 10 hours post-dose. Plasma concentrations of ramipril 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}. The clinical part of the study was conducted between 13 June and 11 July 2012, and the analytical part between 03 July and 06 August 2012.

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 ramipril, n=26.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**12.1 ± 5.2**	**19.0 ± 10.8**	**0.56 (0.17 – 1.33)**
Reference	**11.8 ± 4.9**	**19.5 ± 10.9**	**0.56 (0.33-1.33)**
***Ratio % (90% CI)**	**101.2 (91.9 – 111.5)**	**96.1 (80.1 – 115.3)**	**-**
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 Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Study “19-44-152-11-05-21” /”RAMIAIS 03/2020” – 5 mg tablet
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing ramipril, 5 mg, tablet with TRITACE, 5 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours post-dose. Plasma concentrations of ramipril were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and Cmax. The clinical part of the study was conducted between 22 July and 09 August 2021, and the analytical part between 14 September and 27 September 2021.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ramipril, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**9.53 ± 4.55**	**11.2 ± 6.1**	**0.50 (0.33 – 2.33)**
Reference	**9.83 ± 4.09**	**11.8 ± 6.0**	**0.58 (0.33 – 2.66)**
***Ratio % (90% CI)**	**95.89 (91.04 – 101.00)**	**94.97 (83.83 – 107.59)**	**-**
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 Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Biowaiver – 2.5 mg tablet
A biowaiver was sought for the additional strength of 2.5 mg.

Discussion and overall conclusion
The bioequivalence studies and their statistical evaluations 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 of the 10 mg tablet study (RAMIAIS 04/2012) and the 5 mg tablet study (RAMAIS 03/2020) have been adequately validated in accordance with the standards of ICH guideline M10 on bioanalytical method validation and study sample analysis.

The pharmacokinetics of ramiprilat are linear after doses of 2.5 mg and 5 mg. From a pharmacokinetic point of view it is thus considered acceptable not to perform a separate bioequivalence study with the lower tablet strength.

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.

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 Ramiliv.

Safety specification
The MAH has submitted the version 01 RMP dated 30.09.2021 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	1. Hyperkalaemia 2. (Symptomatic) hypotension 3. Hypersensitivity reactions incl. angioedema 4. Foetotoxicity 5. Renal failure
Important potential risks	Not identified
Missing information	1. Exposure during breast feeding

Assessor's comment: The version 01 of the RMP is in line with the published RMP on CMDHs website (*List of safety concerns per approved Risk Management Plan (RMP) of active substances per product (June 2021*)) and is endorsed by the RMS.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 01 signed 30.09.2021 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 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 PL was Romanian.

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, Ramiliv, is found adequate. There are no objections to approval of Ramiliv, 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 Ramiliv, 2,5 mg, 5 mg, 10 mg, Tablet was positively finalised on 2024-03-18.

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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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