LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lisiliv
(lisinopril dihydrate)

SE/H/2070/01-02/DC

This module reflects the scientific discussion for the approval of Lisiliv. The procedure was finalised on 2021-07-13. 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 Lisiliv, 10 mg, 20 mg, Tablet.

The active substance is lisinopril dihydrate. 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 Lisiliv, 10 mg and 20 mg, tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Antibiotice SA, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Denmark as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Zestril, 10 mg, tablets, authorised in NL since 1988, with AstraZeneca BV as marketing authorisation holder.

The reference product used in the bioequivalence study is Zestril, 20 mg, tablets from UK with AstraZeneca UK Limited 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

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance 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 Lisiliv 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 Lisiliv 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 Lisinopril with the reference product Zestril.

Pharmacokinetic properties of the active substance
Absorption: Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with interpatient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Elimination: Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours.

Study
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers (27 completed), comparing Lisinopril, 20 mg, tablet with Zestril, 20 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of lisinopril were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 16th April 2015 and 10th June 2015.

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 lisinopril, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**686.2 ± 331.3**	**54.7 ± 27.7**	**6.50 (5.00, 7.50)**
Reference	**677.1 ± 340.9**	**53.6 ± 31.9**	**6.50 (5.00, 7.50**
***Ratio (90% CI)**	**101.6 (88.6-116.5)**	**104.0 (90.3-119.8)**	**-**
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 10 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). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 10 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since there are no indication of non-linear pharmacokinetics (less than proportional than dose) in the therapeutic dose range.

Based on the submitted bioequivalence study, Lisinopril is considered bioequivalent with Zestril.

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 Lisiliv.

Safety specification

The MAH has submitted the version 0.2 RMP dated 31 Aug 2020 and proposed the following summary safety concerns:”

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Hypersensitivity reactions and angioedema 2. Foetotoxicity and neonatal toxicity when used in 2nd and 3rd trimesters of pregnancy
Important potential risks	-
Missing information	-

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 0.2 signed 31 Aug 2020 is considered acceptable.

It is noted that there is no approved RMP for the reference product. Further it is noted no PSUSA has been conducted with a presented Summary of safety concerns and that CMDh has no proposal of voluntary harmonized RMP for this substance. The latest PSUR assessment report are dated before the revision of GVP module V. In accordance with the intention of the updated GVP V (rev 2) it is proposed that the summary of safety concerns will be those included in the Safety specification as indicated above.

The Applicant is asked to update the RMP in accordance with a Summary of safety concerns in PSUSA or harmonized RMP whichever comes first.

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 PIL 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, Lisiliv, is found adequate. There are no objections to approval of Lisiliv, 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 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 Lisiliv, 10 mg, 20 mg, Tablet was positively finalised on 2021-07-13.

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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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