COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lisinopril Mylan 2.5 mg, 5 mg, 10 mg and 20 mg, tablets

(lisinopril dihydrate)

NL/H/4693/001-004/DC

Date: 24 April 2019

This module reflects the scientific discussion for the approval of Lisinopril Mylan 2.5 mg, tablets. The procedure was finalised at 17 March 2011 with Sweden as RMS (SE/H/1037/001-004/DC). The current RMS is the Netherlands (NL/H/4693/001-004/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lisinopril Mylan 2.5 mg, tablets, from Mylan B.V.

The product is indicated for:

- treatment of hypertension
- treatment of symptomatic heart failure
- short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.
- treatment of renal disease in hypersensitive patients with Type 2 diabetes mellitus and incipient nephropathy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zestril tablets 2.5 mg, 5 mg, 10 mg and 20 mg which has been registered in Sweden by AstraZeneca. In the Netherlands, Zestril has been registered since 13 October 1988 by the procedure SE/H/0527/001-004/DC.

The RMS of the initial procedure was Sweden and the concerned member states (CMS) involved in this procedure were Ireland, the Netherlands, Norway and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

- Lisinopril Mylan 2.5 mg tablets: white to off white, round, biconvex tablet debossed with “L over 22” on one side of the tablet and “M” on the other side. Each tablet contains lisinopril dihydrate equivalent to 2.5 mg anhydrous lisinopril.
- Lisinopril Mylan 5 mg tablets: light pink, mottled, round, biconvex tablet debossed with “L and 23” on either side of the break-line on one side and “M” on the other side. Each tablet contains lisinopril dihydrate equivalent to 5 mg anhydrous lisinopril.
- Lisinopril Mylan 10 mg: light pink, mottled, round, biconvex tablet debossed with “M over L 24” on one side of the tablet and break-line on the other side. Each tablet contains lisinopril dihydrate equivalent to 10 mg anhydrous lisinopril.
- Lisinopril Mylan 20 mg: pink, mottled, round, biconvex tablet debossed with “M over L 25” on one side of the tablet and break-line on the other side. Each tablet contains lisinopril dihydrate equivalent to 20 mg anhydrous lisinopril.

The 5 mg, 10 mg and 20 mg tablets can be divided into equal doses.

And contains as active substance 100 mg of <imatinib>, <as 119 mg> of <imatinib mesilate>.

The tablets are packed in OPA/Al/PVC, PVC/PVdC/Alu and/or HDPE bottles.

The excipients are: calcium hydrogen phosphate dihydrate, mannitol, pregelatinized maize starch, croscarmellose sodium, povidone, magnesium stearate, sodium laurilsulfate, colloidal silicon dioxide and iron oxide red (not included in the 2.5 mg strength)

II.2 Drug Substance

Lisinopril dihydrate has a monograph in the Ph Eur.

Lisinopril dihydrate is a white or almost white, crystalline powder which is soluble in water. The structure of lisinopril dihydrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on solubility, polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Primylis tablets are formulated using excipients described in the current Ph Eur, except for iron oxide red, which is controlled according to the USP/NF. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as aqueous solubility, hygroscopic properties, polymorphism, particle size and stability.

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 specification 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 and data presented support the shelf life claimed in the SPC, with no special storage precautions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lisinopril Mylan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lisinopril Mylan 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zestril which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lisinopril is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

To support the application, the MAH has submitted two single-dose bioequivalence studies in the fasting state with the strengths 5 mg and 20 mg.

20 mg
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 40 (38 completed) healthy male volunteers under fasting conditions. Blood samples were collected up to 72 hours after drug administration and the study periods were separated by a wash-out period of 21 days. The study design is considered satisfactory. Plasma concentrations of lisinopril were determined with a validated LC-MS/MS method. The 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80-125% for AUC0-72 and Cmax.

5 mg
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 40 (38 completed) healthy male volunteers under fasting conditions. Blood samples were collected up to 72 hours after drug administration and the study periods were separated by a wash-out period of 22 days. The study design is considered satisfactory. Plasma concentrations of lisinopril were determined with a validated LC-MS/MS method. The 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80-125% for AUC0-72 and Cmax.

Thus, bioequivalence has been shown for the 5 mg and for the 20 mg strength. Based on previous European approval procedures, the pharmacokinetics of lisinopril appears to be linear in the entire dose range. From a pharmacokinetic perspective, absence of studies with the strengths 2.5 and 10 mg is acceptable.

The results of the conducted bioequivalence studies can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Perindopril 2 mg tablets, NL/H/977/01-03/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lisinopril Mylan 2.5 mg, 5 mg, 10 mg and 20 mg, tablets has a proven chemical-pharmaceutical quality and are generic forms of Zestril tablets 2.5 mg, 5 mg, 10 mg and 20 mg. Zestril is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lisinopril Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 March 2011.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse