LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Primylis (former Lisinopril Jenson)
(lisinopril dihydrate)

SE/H/1037/01-04/DC

This module reflects the scientific discussion for the approval of Primylis. The procedure was finalised at 2011-03-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Jenson Pharmaceutical Services Ltd has applied for a marketing authorisation for Primylis, tablets, 2,5, 5, 10 and 20 mg claiming essential similarity to Zestril tablets 2.5, 5, 10 and 20 mg marketed in Sweden by AstraZeneca. The product contains lisinopril dihydrate as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bio-equivalence studies is Zestril 5 mg and 20 mg tablets marketed by AstraZeneca in France.

II. QUALITY ASPECTS

II.1 Introduction

Primylis is presented in the form of tablets containing lisinopril dihydrate equivalent to 2.5 mg, 5 mg, 10 mg and 20 mg, respectively, of lisinopril. 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). The tablets are packed in Al/Al-blister, PVC/PVdC/Al-blister or HDPE bottle with polypropylene cap and silica gel desiccant.

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.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

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

The study with the 20 mg strength was performed at Veeda clinical research Pvt. Ltd., Ambawadi, Ahmedabad, India. 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 AUC_{0-72} and C_{max}.

The study with the 5 mg strength was a single-dose bioequivalence study in the fasting state performed at Veeda clinical research Pvt. Ltd., Ambawadi, Ahmedabad, India between 11th March and 6th April 2010. 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 AUC_{0-72} and C_{max}.

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.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

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.

The risk/benefit ratio is considered positive and Primylis, tablets, 2,5, 5, 10 and 20 mg are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Primylis, tablets, 2,5, 5, 10 and 20 mg was successfully finalised on 2011-03-17.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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