CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lisinopril 30 PCH, 30 mg tablets Pharmachemie B.V., the Netherlands

lisinopril dihydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 33797

6 September 2010

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA03
Route of administration:	oral
Therapeutic indication:	hypertension; symptomatic heart failure; short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, and treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.
Prescription status:	prescription only
Date of authorisation in NL:	4 December 2008
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Lisinopril 30 PCH, 30 mg tablets from Pharmachemie B.V. The date of authorisation was on 4 December 2008 in the Netherlands.

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 hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.

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

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

This national application for marketing authorisation concerns Lisinopril 30 PCH, 30 mg tablets. The application is made in accordance with article 10(3) of Directive 2001/83/EC, hybrid application and concerns a line extension of Lisinopril 20 PCH, 20 mg tablets, with a difference in strength. Lisinopril 20 PCH has been registered in the Netherlands since 5 September 2002 under NL License RVG 26333. Lisinopril 20 PCH was authorised as a generic form of the innovator product Zestril-20, 20 mg tablets.
The 30 mg Zestril tablet is also available in the Netherlands: Zestril-30 (NL RVG 24015) has been registered since 17 March 2000 by AstraZeneca B.V.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 20 mg product is compared with the pharmacokinetic profile of the reference product Carace 20 mg tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. No bioequivalence study has been conducted with the Lisinopril 30 PCH. A biowaver could be granted, as the 30 mg tablet is dose proportional to the 20 mg tablet from the same registration holder. This hybrid product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is lisinopril dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is soluble in water, sparingly soluble in methanol, and practically insoluble in acetone and ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional specifications of the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability of drug substance
Based on the submitted results of stability studies, a re-test of 3 years has been set for the active substance, with no specific storage conditions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Lisinopril 30 PCH is a white, oval tablet with imprint "LSN 30" on one side.

The tablets are packed in PVC/PVDC/Alu blisters.

The excipients are: pregelatinized maize starch, maize starch, anhydrous calcium hydrogen phosphate (E341), mannitol (E421) en magnesium stearate (E470B).

Pharmaceutical development
The development of the product is satisfactory performed. The excipients used are common for immediate release tablets. The packaging is suitable for the drug product. Bio-equivalence studies have been done with the 20 mg tablets. The 30 mg tablets are dose proportional to these tablets (1.5x factor). Dissolution data have demonstrated that the tablets are comparable.

Manufacturing process

The tablets are manufacture by straightforward wet granulation process. The manufacturing process has been sufficiently described. Validation data have been provided on three full-scale batches of batches from the manufacturing site.

Control of excipients
All excipients comply with their Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, weight, uniformity of weight, content uniformity, assay, dissolution, related substances, disintegration, identification, resistance for crushing, and microbial quality. These requirements are suitable. Satisfactory validation data for the analytical methods have been provided. Results of batch analysis on three batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the finished product have been provided in compliance with ICH Guidelines under long term conditions at 25°C/60% RH (9 months) and under accelerated conditions at 40°C/75% RH (6 months). The product was packaged in the proposed blisters. No significant changes were observed.
In addition, supportive stability data were provided on other strengths (2.5, 5, 10 and 20 mg), covering up to 24 months. The tablets are virtually identical to the existing 20 mg tablets and very much like the lower strengths. The supportive data are therefore acceptable to confirm the stability claim. A shelf-life of 24 months could be granted. The applicable storage condition is 'Store below 30°C'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This active substance has been available on the Dutch market since 1988. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of lisinopril released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Lisinopril is a well-known active substance with established efficacy and tolerability.

Bioequivalence study
For this hybrid application, the MAH did not submitted a bioequivalence study. Instead the MAH proposed a biowaiver. After a change in the formulation the biowaiver was accepted, see below.

Extrapolation from 20 mg to 30 mg strength
The MAH applied for a biowaiver and argued that no new bioequivalence study would be necessary for the new lisinopril 30 mg tablet, as the 30 mg tablet is qualitatively and proportionally identical to the 20 mg tablet. This was however not agreed upon, as the 20 and 30 mg lisinopril tablets are not dose proportional. As a consequence, the results from the bioequivalence study performed with the 20 mg lisinopril tablet can not be extrapolated to the 30 mg tablet. According to the Note for Guidance, the ratio between amounts of active substance and excipients is the same or, in case of a low concentration of active substance (less than 5%), the ratio between the amounts of excipients is similar. This is not the

case here, as the percentage of active ingredients is 10% and 15% for the 20 and 30 mg lisinopril tablets, respectively.
In response to this major objection from the MEB, the MAH adapted the 30 mg tablet to be completely dose proportional with the already registered 20 mg tablet. The biowaiver could then be granted for the 30 mg tablet, as all requirements were met: the different strengths have a similar formulation and the manufacturing process is the same. The dissolution profile of the tablets is similar and the pharmacokinetics of lisinopril are linear.

Risk management plan
Lisinopril was first approved in 1988, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lisinopril can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC is in line with the earlier approved Lisinopril PCH tablets.

Readability test
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 test consisted of two rounds with 10 participants each. After the first test round, some revisions were made to the PIL in order to improve findability of relevant information. Also, a short explanation of the term *angio-oedema* was added. In the second test round, no difficiencies were identified. The overall readability score of the PIL was 86% in the first round, and 89% in the second round. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lisinopril 30 PCH, 30 mg tablets has a proven chemical-pharmaceutical quality and is an approvable hybrid form of Lisinopril 20 PCH, 20 mg tablets. Lisinopril 20 PCH was registered on 5 September 2002 as a generic form of Zestril-20 tablets.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents; the results of a bioequivalence study with the 20 mg strength also apply to the 30 mg tablet.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other lisinopril containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that Lisinopril 30 PCH is a legitimate line extension of Lisinopril 20 PCH, and has therefore granted a marketing authorisation. Lisinopril 30 PCH, 30 mg tablets was authorised in the Netherlands on 4 December 2008.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached