PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Lisinopril 5/10/20 Focus, tablets 5/10/20 mg
Focus Care Pharmaceuticals B.V., the Netherlands

lisinopril (as 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 and its fellow -organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/970/01-03/MR
Registration number in the Netherlands: RVG 33563, 33564, 33565

Date of first publication: 16 April 2008
Last revision: 30 August 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: 16 March 2006
Concerned Member States: Mutual recognition procedure with UK.
Application type/legal basis: Directive 2001/83/EC article 10(1)

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 member states have granted a marketing authorisation for Lisinopril 5 Focus, 5 mg tablet, Lisinopril 10 Focus, 10 mg tablet, and Lisinopril 20 Focus, 20 mg tablet, from Focus Care Pharmaceuticals B.V. The first date of authorisation was on 16 March 2006 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, and 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 Focus tablets 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 application concerns a generic application claiming essential similarity with the innovator products Zestril 5, 10 and 20 mg (NL license RVG 12560, 12561 and 12562) which have been registered in the Netherlands by AstraZeneca since 1988. In addition, reference is made to Zestril authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) 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 product is compared with the pharmacokinetic profile of the reference product Acerbon 20 mg, registered in Germany. Acerbon is the name for the innovator product in Germany. 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. This generic 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.
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 these product types 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 and excipients
The active substance is lisinopril dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Lisinopril dihydrate is readily soluble in water and acidic solutions and is therefore an active ingredient with good solubility.

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, and 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 Ph.Eur.

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. with one additional specification indicated in the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
No specific re-test period is indicated on the CEP. Therefore, stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 5 years when stored in double polyethylene bags without 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 5 Focus, Lisinopril 10 Focus and Lisinopril 20 Focus contain as active ingredient lisinopril anhydrous (5, 10 and 20 mg) corresponding to 5.445, 10.890 and, 21.780 mg lisinopril dihydrate, respectively.

Lisinopril 5 Focus, 5 mg tablets are white, round biconvex tablets with 5 on one side and a score on the other side.
Lisinopril 10 Focus, 10 mg tablets are white, round biconvex tablets with 10 on one side and a score on the other side.
Lisinopril 20 Focus, 20 mg tablets are white, round biconvex tablets with 20 on one side and a score on the other side.

The tablets are supplied in PVC/PVDC-Aluminium blister foils.

The excipients are: mannitol, calcium hydrogen phosphate dihydrate, maize starch, pregelatinised maize starch, magnesium stearate, and colloidal anhydrous silicon.
The excipients are well known and safe in the proposed concentrations.

**Pharmaceutical development**
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging is suitable for the product. The objective was to develop a product that would be bioequivalent with the innovator product Zestril.

**Manufacturing process and quality control of the medicinal product**
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 4 batches of all three strengths in accordance with the relevant European guidelines.

**Excipients**
The excipients used are common for immediate release tablets. All excipients comply with the relevant Ph.Eur. specifications.

**Quality control of drug product**
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for breakability, description, weight, uniformity of weight, content uniformity, assay, dissolution, related substances, disintegration, identification, resistance for crushing, and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

**Stability tests on the finished product**
Stability data on the product have been provided for 21 batches in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. Based on the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: “Do not store above 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 product is a generic formulation of Zestril, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Lisinopril 20 Focus is compared with the pharmacokinetic profile of the German reference product Acerbon 20 mg. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The preparation of the bioequivalence batch is identical to preparation proposed for marketing.

The bio-equivalence study has been performed with slightly different tablets. These tablets differ from the current composition by the amount of magnesium stearate compensated by calcium hydrogen phosphate. Dissolution data have demonstrated that this difference does not result in different dissolution. In view of this and the rapid dissolution of the tablets at pH 1, 4 and 6.8, the results of the bioequivalence study are considered valid for the current formulations.

Setup
A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-45 years. Each subject received daily a single dose (20 mg) of one of the 2 lisinopril formulations. The tablet was orally administered with 240 ml water after fasting. For each subject there were 2 dosing periods, separated by a washout period of 28 days. Two subjects were withdrawn from the study. The bioavailability of the test Lisinopril 20 Focus, 20 mg tablet was compared to the German reference product Acerbon 20 mg tablet (Zeneca, Germany). Blood samples were taken predose and at 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 48, 72, 96, 120, 168, and 216 hours after administration of the products.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-t} ng.h/ml</th>
<th>AUC\text{0-\infty} ng.h/ml</th>
<th>C\text{max} ng/ml</th>
<th>t\text{max} h</th>
<th>t\text{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1096 ± 366</td>
<td>1204 ± 421^*</td>
<td>68 ± 26</td>
<td>6.0 (4.0-9.0)</td>
<td>119 ± 29^*</td>
</tr>
<tr>
<td>Reference</td>
<td>1085 ± 342</td>
<td>1214 ± 380^‡</td>
<td>69 ± 23</td>
<td>6.0 (4.0-10.0)</td>
<td>119 ± 29^‡</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.00 (0.89-1.12)</td>
<td>--</td>
<td>0.97 (0.81-1.13)</td>
<td>--</td>
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</tr>
<tr>
<td>CV (%)</td>
<td>22.2</td>
<td>--</td>
<td>32.1</td>
<td>--</td>
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</tr>
</tbody>
</table>

AUC\text{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\text{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C\text{max} maximum plasma concentration
t\text{max} time for maximum concentration
t\text{1/2} half-life

*ln-transformed values

The 90% confidence interval and the Coefficient of Variation (CV) of AUC\text{0-\infty} were not calculated, because for some subjects no elimination constant could be determined, which is necessary for the calculation of the AUC\text{0-\infty}. For the same reason, the number of subjects is 14 and 15 for the AUC\text{0-\infty} from the test tablet and reference tablet, respectively.
Blood samples were taken till 216 hours after administration. In this time frame absorption of the tablet has already taken place. Therefore, the \( \text{AUC}_{0-\infty} \) is not required to show bioequivalence.

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \) are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of lisinopril under fasting conditions, it can be concluded that test Lisinopril 20 Focus, 20 mg tablet and the German reference Acerbon 20 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Extrapolation of results**

The 5 mg and 10 mg tablets are dose proportional with the 20 mg tablets, except for the quantity of calcium hydrogen phosphate. No bioequivalence study is necessary for the 5 and 10 mg tablets, because the pharmacokinetics of lisinopril dihydrate is linear, the qualitative composition is the same, the ratio of the excipients is the same (in case of small strengths), both products are produced by the same manufacturer at the same production site and the dissolution rate in vitro is the same under identical test conditions. Therefore, the results of the bioequivalence study performed with the 20 mg tablet also apply to the 5 mg and 10 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk Management Plan**

Lisinopril dihydrate 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 dihydrate 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 content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Zestril marketed by AstraZeneca BV. Post-approval, the SPC was brought in line with the agreed CSP attached to the Final PSUR AR for worksharing of lisinopril/Zestril covering the period from 24/09/2004 to 23/09/2007. See variation NL/H/0970/001-003/I/004 in the ‘steps taken after finalisation of the initial procedure’ table.

**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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lisinopril 5 Focus, Lisinopril 10 Focus and Lisinopril 20 Focus, respectively 5, 10 and 20 mg tablets, have a proven chemical-pharmaceutical quality and are generic forms of Zestril 5, 10 and 20 mg tablets. 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 SPC is consistent with that of the reference product.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. On the basis of the data submitted, the concerned member states considered that bioequivalence has been demonstrated for Lisinopril 5 Focus, Lisinopril 10 Focus and Lisinopril 20 Focus with the reference product and have therefore granted a marketing authorisation.

There was no discussion in the CMD. Agreement between member states was reached during a written procedure.

The first PSUR will cover the period from 21 March 2007 till 21 March 2010.

The date for the first renewal will be 21 March 2012.

The following post-approval commitments have been made during the procedure:

**Quality**

- Cross-validation data for all sites where analysis is performed will be submitted before the product is launched on the UK market.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/n on approval</th>
<th>Assessment report attached</th>
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<td>Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a new manufacturer. Other substances.</td>
<td>NL/H/0970/001-003/IA/001</td>
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<td>13-6-2007</td>
<td>27-6-2007</td>
<td>Approval</td>
<td>N</td>
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<td>Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance. Tightening of specification limits. Addition of a new test parameter to the specification of an active substance.</td>
<td>NL/H/0970/001-003/IB/002</td>
<td>IB</td>
<td>13-6-2007</td>
<td>13-7-2007</td>
<td>Approval</td>
<td>N</td>
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<td>Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marketing.</td>
<td>NL/H/0970/001-003/IA/003</td>
<td>IA</td>
<td>9-11-2007</td>
<td>23-11-2007</td>
<td>Approval</td>
<td>N</td>
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<td>To bring the SPC and PIL in line with the agreed CSP attached to the Final PSUR AR for worksharing of lisinopril/Zestril covering the period from 24/09/2004 to 23/09/2007.</td>
<td>NL/H/0970/001-003/II/004</td>
<td>II</td>
<td>2-9-2008</td>
<td>4-3-2009</td>
<td>Approval</td>
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<td>Change in the name and address of the MAH for UK only.</td>
<td>NL/H/0970/001-003/IA/005</td>
<td>IA</td>
<td>28-11-2008</td>
<td>12-12-2008</td>
<td>Approval</td>
<td>N</td>
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<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Not including batch control/testing.</td>
<td>NL/H/0970/001-003/IA/006</td>
<td>IA</td>
<td>24-11-2008</td>
<td>8-12-2008</td>
<td>Approval</td>
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