

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Lisinopril Aurobindo 5 mg, 10 mg, 20 mg, 30 mg and 40 mg,
tablets**

Aurobindo Pharma (Malta) Limited, Malta

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 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/1976/001-005/MR

Registration number in the Netherlands: RVG 100687, 32683-32686

30 August 2010

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA03
Route of administration:	oral
Therapeutic indication:	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 diabetes mellitus and incipient nephropathy.
Prescription status:	prescription only
Date of first authorisation in NL:	18 March 2009 (5 mg); 27 March 2007 (other strengths)
Concerned Member States:	Mutual recognition procedure with DE, IT, PT, 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 Aurobindo 5 mg, 10 mg, 20 mg, 30 mg and 40 mg, tablets from Aurobindo Pharma (Malta) Limited. The date of authorisation in the Netherlands was on 18 March 2009 for the 5 mg tablet, and on 27 March 2007 for the other strengths.

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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Zestril 5, 10, 20, 30 and 40 mg tablets (NL License RVG 12560-12562, 24015 and 12563, respectively) which have been registered in the Netherlands by AstraZeneca B.V. since 1988 (5, 10, 20, 40 mg) and 1990 (30 mg). Zestril authorisations in the individual member states have been harmonised through MRP SE/H/0527/001-005.

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 two bioequivalence studies in which the pharmacokinetic profile of the 5 mg and 20 mg products is compared with the pharmacokinetic profile of the reference products Zestril 5 mg and 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. These generic products can be used instead of their reference products.

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 generic 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

The active substance is lisinopril, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white crystalline powder, which is soluble in water, sparingly 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 drug substance specification is in line with the Ph.Eur. and its additional requirements on any other impurities and residual solvents. The MAH has added a test and limit for particle size, bulk density and microbial aspect. The in-house methods have been sufficiently described and validated. Batch analytical data have been provided on three batches, demonstrating compliance with the specification.

Stability of drug substance

The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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 Aurobindo 5 mg are light red coloured, round shaped, biconvex, uncoated tablets debossed with "L" on one side and other side with '5' on one side of the score line. The tablet can be divided into equal halves.

Lisinopril Aurobindo 10 mg are light yellow coloured, round shaped, biconvex, uncoated tablets, debossed with 'L' on one side and on other side with '10'.

Lisinopril Aurobindo 20 mg are light yellow coloured, capsule shaped, biconvex, uncoated tablets, debossed with 'L' on one side and on other side with '20'.

Lisinopril Aurobindo 30 mg are light yellow coloured, round shaped, uncoated tablets, debossed with 'L' on one side and on other side with '30'.

Lisinopril Aurobindo 40 are light yellow coloured, capsule shaped, biconvex, uncoated tablets, debossed with 'L' on one side and on other side with '40'.

The tablets are packed in transparent PVC-PVdC/aluminium blisters.

The excipients are: calcium hydrogen phosphate, maize starch, mannitol, pregelatinised maize starch, magnesium stearate, iron oxide red (5 mg), iron oxide yellow (10/20/30 and 40 mg).

The formulation of the 5 mg and 10 mg tablets have the same tablet weight. Only the amounts of lisinopril and calcium hydrogen phosphate are different. The 10 mg, 20 mg, 30 mg and 40 mg tablets are dose proportional.

Pharmaceutical development

The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of tablet formulations and most are also present in the innovator product. The packaging materials are usual and suitable for the product at issue. Dissolution of test and innovator tablets was studied, showing fast release in all dissolution media used. Furthermore, the dissolution profiles are similar for all strengths. The UK reference product used in the bioequivalence study is acceptable from a chemical-pharmaceutical point of view. The 5 mg tablets contain a score line. Subdivision of tablets was tested and demonstrated to be within the acceptance criteria set as per Ph.Eur. The pharmaceutical development has been described in sufficient detail.

Manufacturing process

The tablets are prepared by a wet granulation process followed by compression of the tablets. This is considered a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches (blend) and two product-scale batches (tablets).

Control of excipients

The excipients comply with the Ph.Eur or USP and some additional requirements. These specifications are acceptable.

Quality control of drug product

The product specification for the tablets is in line with Ph.Eur. requirements for tablets and has been compared with the BP monograph on lisinopril tablets. The product specification includes tests for description, identification, average weight, uniformity of dosage units, dissolution, related substances, assay, water, thickness, microbiological purity, and identification of colorants. The shelf-life limits for average weight, dissolution, one impurity, total impurities and water content slightly differ from the release limits. The analytical methods have been adequately described and validated. Batch analysis results have been provided of two pilot-scale batches of each tablet strength; all results comply with the proposed specification.

Stability of drug product

The tablets have been stored at 30°C/70% RH (48 months) and 40°C/75% RH (6 months) in PVC-PVdC/aluminium blisters. The stability results show that the water content tends to increase. The assay values show an increase as well as decrease, whereas the content of impurities increases. For all parameters investigated the results remain within the shelf-life requirements. The absence of a special storage condition regarding temperature is therefore acceptable. A shelf-life of 48 months, without special storage conditions has been granted.

The MAH committed to submit stability results of production-scale batches when available.

Several other commitments have been made with regard to the finished product; these can be found on page 8 of this report.

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 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.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Lisinopril Aurobindo 5 mg and 20 mg tablets (Aurobindo Pharma Limited, Malta) is compared with the pharmacokinetic profile of the reference product Zestril 5 mg and 20 mg tablets (AstraZeneca, UK).

The choice of the reference product

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Bioequivalence study I – 5 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-35 years. Each subject received a single dose (5 mg) of one of the 2 lisinopril formulations.

The tablet was orally administered with 240 ml water after a fasting period of 11 hours. Food was not allowed for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 20, 24, 30, 36, and 48 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One volunteer was withdrawn from the study due to hypotension at t=7.5 hours. Thirty-five subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of lisinopril under fasted conditions.

Treatment N=35	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	291.9 \pm 87.5	330.8 \pm 90.4	17.5 \pm 6.8	7.5	--
Reference	307.7 \pm 95.2	342.8 \pm 92.1	18.8 \pm 7.1	7.5	--

*Ratio (90% CI)	0.95 (0.87- 1.05)	0.97 (0.89-1.05)	0.93 (0.83-1.04)	--	--
CV (%)	23	20	29	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity 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 concentration t_{1/2} half-life					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of lisinopril under fasted conditions, it can be concluded that Lisinopril Aurobindo 5 mg and Zestril 5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – 20 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 34 (+ 4 standby) healthy male subjects, aged 18-34 years. Each subject received a single dose (20 mg) of one of the 2 lisinopril formulations. The tablet was orally administered with 240 ml water after a fasting period of 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 20, 24, 30, 36, and 48 hours after administration of the products.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

In the first study period one subject withdrew consent and was withdrawn from the study. In the second study period one subjects withdrew consent. Two others did not show up for the start of the second part of the study. These subjects were withdrawn. Three of the withdrawn subjects were replaced by a standby subject who had received the same same sequence as the replaced subjects. Consequently data of 33 subjects were included in the pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lisinopril under fasted conditions.

Treatment N=35	AUC_{0-t} ng.h/ml	AUC_{0-∞} ng.h/ml	C_{max} ng/ml	t_{max} h	t_{1/2} h
Test	1618 ± 674	1653 ± 673	108 ± 47	8.0 (4.0-8.0)	7.1 ± 0.8
Reference	1790 ± 698	1830 ± 701	117 ± 46	6.0 (4.0-10.0)	7.3 ± 5.9
*Ratio (90% CI)	0.89 (0.83-0.97)	0.89 (0.83-0.97)	0.91 (0.84-0.99)	--	--
CV (%)	20.41	19.85	20.96	--	--

AUC_{0-∞}	area under the plasma concentration-time curve from time zero to infinity
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 concentration
t_{1/2}	half-life

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of lisinopril under fasted conditions, it can be concluded that Lisinopril Aurobindo 20 mg and Zestril 20 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Lisinopril may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of lisinopril. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths

The results of the bioequivalence study performed with the 20 mg tablet can be extrapolated to the 10, 30 and 40 mg tablets. All these strengths have a similar formulation and the manufacturing process is the same. The dissolution profile of all tablets is similar and the pharmacokinetics of lisinopril are linear.

The MEB has been assured that the bioequivalence studies have 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 was first approved in 1987, 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 post authorisation 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 SPC of innovator Zestril registered via the MRP procedure SE/H/0527/001-004 and is approvable.

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead, a bridging study was provided in accordance with the requirements of Article 59(3) of Council Directive 2001/83/EC. Therefore the bridging for the Lisinopril Aurobindo PIL, without the need for a full consultation test is considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lisinopril Aurobindo 5 mg, 10 mg, 20 mg, 30 mg and 40 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Zestril 5, 10, 20, 30 and 40 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 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. Lisinopril Aurobindo 5 mg, 10 mg, 20 mg, 30 mg and 40 mg, tablets were authorised in the Netherlands on 16 November 2009.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lisinopril Aurobindo 5 mg, 10 mg, 20 mg, 30 mg and 40 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 1 July 2010.

A European harmonised birth date has been allocated (24 September 1987) and subsequently the first data lock point for lisinopril is September 2010. The first PSUR will cover the period from July 2010 to September 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 16 November 2014.

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

Quality - medicinal product

- The MAH committed to perform validation on the maximum tablet batch sizes of the 20 mg, 30 mg and 40 mg tablets.
- The MAH committed to conduct validation on the first three commercial batches manufactured at maximum tablet batch size for the 5 mg product.
- The MAH committed to place the first three commercial batches on long term and accelerated stability studies. The first three batches of each strength with maximum batch size shall also be kept on stability. The stability studies will be continued up to the proposed shelf life. One marketed batch of each packaging size will be included in long term stability studies per year.
- The MAH committed to include specified mixing speeds in the validation studies. The mixing speed applied for the larger production scaled batches will be determined during the validation studies with production-scale batches.

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 _{1/2}	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