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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kaliumlosartan Alet 12.5/50/100 mg film-coated tablets
Alet Pharmaceuticals S.A., Greece

losartan (as potassium)

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/1561/001-003/MR
Registration number in the Netherlands: RVG 34409, 34411, 34412

13 October 2009

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA01
Route of administration:	oral
Therapeutic indication:	essential hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment; chronic heart failure (in patients ≥ 60 years) when treatment with ACE inhibitors is not considered suitable due to incompatibility or contraindication; reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.
Prescription status:	prescription only
Date of first authorisation in NL:	21 April 2008
Concerned Member States:	Mutual recognition procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) for 50 and 100 mg, 10(3) for 12.5 mg

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 Kaliumlosartan Alet 12,5/50/100 mg film-coated tablets, from Alet Pharmaceuticals S.A. The date of authorisation was on 21 April 2008 in the Netherlands.

The product is indicated for treatment of:

- essential hypertension.
- renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
- reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.

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

Losartan is a synthetic oral angiotensin-II receptor (type *AT1*) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the *AT1* receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.
Losartan selectively blocks the *AT1* receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.
Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.
Both Losartan and its principal active metabolite have a far greater affinity for the *AT1*-receptor than for the *AT2*-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cozaar 50 mg and 100 mg tablets, registered in the Netherlands (NL license RVG 17617 and 26791) by Merck Sharp & Dohme B.V. since 1995 and 2002, respectively. In addition, reference is made to the Lorzaar authorisation in Germany (reference product).

The marketing authorisation is granted based on article 10(1) (50 mg & 100 mg) and 10(3) (12.5 mg) of Directive 2001/83/EC. The application for the 12.5 mg strength is according to 10(3) hybrid application, because at the time of application, the 12.5 mg strength was not registered for the innovator product.

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 Lorzaar 100 mg tablets, registered 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. These generic products can be used instead of their 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.

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 losartan, an established active substance described in the Ph.Eur.* The active substance is freely soluble in water and it shows polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The active substance is manufactured in 5 steps. A clear list with potential impurities is included. The manufacturing process is appropriately described in the submitted documentation. The losartan potassium produced by the DMF-holder contained only one polymorphic form. The spectra of three batches are included in the dossier which show consistency of the polymorphic form.

Quality control of drug substance
The drug substance specification provided by the MAH is in line with the Ph.Eur., with additional requirements for residual solvents. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for five production scale batches.

Stability
The MAH refers to the DMF for information regarding the packaging material and stability. The following has been shown by the DMF-holder: Stability data on the active substance have been provided for three production scale batches stored at 25ºC/60%RH (36 months) and 40ºC/75%RH (6 months). The batches were adequately stored. Slight upward trends were seen in total impurities and water content at accelerated and long-term storage conditions, but values are within specifications up to 6 and 36 months, respectively.

** 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
The products at issue are losartan film-coated tablets for oral administration. The tablets contain 12.5 mg (11.44 mg losartan), 25 mg (22.9 mg losartan), 50 mg (45.8 mg losartan) or 100 mg (91.6 mg losartan) losartan potassium. The tablets' appearance is as follows:

- *12.5 mg tablet*: white, round, biconvex film-coated tablets with a diameter of 5.1 mm approximately, thickness limited to 2.27 mm.
- *50 mg tablet*: white, round, biconvex film-coated tablets with a diameter of 7.6 mm approximately, bearing a breakline on one side. The tablet can be divided into equal halves.
- *100 mg tablet*: white, round, biconvex film-coated tablets with a diameter of 9.1 mm approximately, bearing a breakline on one side. The tablet can be divided into equal halves.

The excipients used in these tablets are microcrystalline cellulose, lactose monohydrate, pregelatinised maize starch, sodium starch glycolate Type A and magnesium stearate. Each tablet strength is coated with opadry white. The 50 and 100 mg tablets have a break-line on one side. The excipients and packaging are common for this type of dosage form. The contents of the tablets are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH has based the formulation of the composition of the innovator product. In addition the product for registration was tested both *in-vitro* and *in-vivo* against the innovator product. The manufacturing process development of the product has been adequately performed.

Excipients
The excipients comply with the Ph.Eur.*, except opadry. However, opadry is a common coating agent, which comprises of Ph.Eur. excipients. The proposed specifications for the excipients are therefore acceptable.

Manufacturing process
The tablets are produced by direct compression followed by spraying with the coating solution.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scale batches per tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Product specification
The product specification includes tests for description, identification, water content, average weight, disintegration, dissolution, resistance to crushing, uniformity of dosage units, breakability, assay, related substances and microbiological tests. There are some differences in the release and shelf life specifications. All methods are adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot scale batches, demonstrating compliance with the release specification.

Stability tests on the finished product
Stability data on the product have been provided on three batches per tablet strength stored in PVC/PE/PVDC/Alu blister at 25ºC/60%RH (36 months), 30ºC/65%RH (12 months) and 40ºC/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Stability studies are also performed with batches stored in bulk PE-bag in PP container (25ºC/60%RH (12 months) and 40ºC/75%RH (3 months)).
The proposed storage condition and shelf life are acceptable, based on the submitted stability data:
36 months, when packed in PVC/PE/PVDC/Alu-white opaque blisters, with no additional storage conditions. The blisters are subsequently packed in cardboard boxes.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

** 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.*

II.2 Non clinical aspects

This product is a generic formulation of Lorzaar tablets, which are 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 losartan 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Kaliumlosartan Alet 100 mg film-coated tablets (Alet Pharmaceuticals S.A., Greece) is compared with the pharmacokinetic profile of the German reference product Lorzaar 100 mg tablets (Merck, Sharp & Dome, Germany).

The choice of the batches in the bioequivalence study
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 formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The product for registration and the German reference product have a similar dissolution profie.

Study design
An open label, two-way crossover, controlled, randomised, single dose bioequivalence study was carried out under fasted conditions in 70 healthy male (34) and female (36) volunteers, aged 18-42 years. Each subject received a single dose (100 mg) of one of the 2 losartan formulations. The tablet was orally administered with 200 ml water after a fasting period of at least 10 hours. Light meals were used 6 hours after dosing. There were 2 dosing periods, separated by a washout period of 13 days. Blood samples were collected predose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.0, 10.0, 12.0, 16.0, 24.0, 30.0 and 36.0 hours after administration of the products.
All 70 subjects were eligible for pharmacokinetic analysis.

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

Losartan may be administered with or without food. From the literature it is known that food does not interact with the absorption of losartan. 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.

Results
The pharmacokinetic parameters of losartan are provided in the table below. The data of the main metabolite of losartan, losartan carboxy acid, were considered supportive.

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

Treatment N=70	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1090 ± 581	1126 ± 599	738 ± 387	1.10 (0.25-2.5)	2.36 ± 1.75
Reference	1082 ± 528	1119 ± 541	719 ± 351	1.17 (0.5– 3.0)	2.48 ± 1.48
***Ratio (90% CI)**	0.99 0.94 – 1.03	0.99 0.94 – 1.04	1.01 0.91 – 1.12	---	---
CV (%)	16.1	16.0	37.1	---	---

$AUC_{0-\infty}$ 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

**ln-transformed values*

Discussion
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 losartan under fasted conditions, it can be concluded that Kaliumlosartan Alet 100 mg film-coated tablets and the reference Lorzaar 100 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. The data of the main metabolite, losartan carboxy acid, showed the same results as the parent compound losartan.

The 12.5 and 50 mg tablets are dose proportional with the 100 mg tablets. The pharmacokinetics of the active substance are linear. The results of the bioequivalence study performed with the 100 mg tablets therefore apply to the other strengths.

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
Losartan was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of losartan 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
During the mutual recognition procedure, the SPC and package leaflet were brought in line with the article 30 referral texts for Cozaar tablets.

Readability test
The MAH has not submitted a readability test for this procedure, which is acceptable since the proposed Losartan package leaflet (PIL) layout is identical to the layout of Losartan+HCTZ PIL registered by the same MAH's as this has been approved through the MR procedures NL/H/1429-1432, 1434/01-02/MR.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kaliumlosartan Alet 12.5/50/100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Cozaar 100 mg tablets. Cozaar 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other losartan containing products.

The Board followed the advice of the assessors. Kaliumlosartan Alet 12.5/50/100 mg film-coated talbets were authorised in the Netherlands on 21 April 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kaliumlosartan Alet 12.5/50/100 mg film-coated tablets with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 December 2008.

A European harmonised birth date has been allocated (2 September 1994) and subsequently the first data lock point for losartan is September 2010. The first PSUR will cover the period from 19 December 2008 to September 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 19 December 2013.

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

<u>Quality – medicinal product</u>

- The MAH has committed to perform Process validation of the manufacturing process for full scaled batches post authorisation.

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