CBG MEB

Public Assessment Report

Scientific discussion

Losartankalium Aurobindo 25 mg, 50 mg and 100 mg, film-coated tablets

(losartan potassium)

NL/H/3056/001-003/MR

Date: 22 January 2015

This module reflects the scientific discussion for the approval of Losartankalium Aurobindo 25 mg, 50 mg and 100 mg, film-coated tablets. The procedure was finalised on 30 September 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Losartankalium Aurobindo 25 mg, 50 mg and 100 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated for:
- Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
- Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with Angiotensin-converting enzyme (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 clinically stable and on an established treatment regime for chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cozaar 25, 50 and 100 mg film-coated tablets, which has been registered in the UK by Merck Sharp & Dohme Limited since 15 December 1994.
In the Netherlands Cozaar 50 mg and 100 mg film-coated tablets (NL License RVG 17617 and 26791) have been registered by Merck Sharp & Dohme B.V. since 1995 and 2002, respectively. No Cozaar 25 mg tablet is registered in the Netherlands or any of the concerned member states (CMS), except the UK.

The CMS involved in this procedure were:
- Denmark, Italy, Spain, Sweden, United Kingdom (25, 50 and 100 mg)
- Czech Republic, France, Germany, Ireland, Malta (50 and 100 mg)
- Bulgaria, Cyprus (50 mg only)

The marketing authorisation for Losartankalium Aurobindo 50 mg and 100 mg has been granted pursuant to Article 10(1) of Directive 2001/83/EC. Losartan potassium Aurobindo 25 mg is applied for under Article 10(3) in the involved CMS's, referring to the nationally registered Cozaar 50 mg strength, except for the UK where it is a 10(1) application.

II. QUALITY ASPECTS

II.1 Introduction

Losartankalium Aurobindo 25 mg: white to off-white, oval shaped, biconvex film-coated tablets debossed with '5' and '7' on either side of score line on one side and 'J' with a score line on other side.
Losartankalium Aurobindo 50 mg: white to off-white, oval shaped, biconvex film-coated tablets debossed with 'E' on one side and '4' and '6' separated by score line on the other side.
Losartankalium Aurobindo 100 mg: white to off-white, oval shaped, biconvex film-coated tablets debossed with 'E' on one side and '47' on other side.

The 25 mg and 50 mg tablets bear a score line and can be divided into equal halves.

The film-coated tablets are packed in PVC/PE/PVDC-Aluminium blisters or HDPE bottles closed with polypropylene closure.

The excipients are: microcrystalline cellulose, lactose monohydrate, pregelatinized starch, low substituted hydroxypropyl cellulose, magnesium stearate, hydroxypropyl cellulose, hypromellose and titanium dioxide.

The different strengths are dose proportional.

II.2 Drug Substance

The active substance is losartan potassium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, which is freely soluble in water and in methanol, and slightly soluble in acetonitrile. It shows optical isomerism and polymorphism. Crystalline polymorph form I is used as losartan potassium polymorph form I.

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 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., with additional requirements for identity, particle size distribution and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed regarded optimization studies on the excipient concentrations, characterisation of the originator product and comparative *in-vitro* dissolution studies. A bioequivalence study was performed with the 100 mg drug product. The MAH demonstrated similarity between the dissolution profiles of the 100 mg reference and test batches used in the bioequivalence (BE) study. Furthermore, the additional strengths of drug product (i.e. 25 mg and 50 mg) were demonstrated to have similar dissolution profiles compared to the 100 mg test batch used in the BE studies. The composition and manufacturing process of the batch used in the BE study is similar to the finalized drug product.
The suitability of the break-marks on the 25 mg and 50 mg tablets to subdivide the tablets in equal halves was demonstrated in compliance with the applicable Ph.Eur. test. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of dry mixing, wet granulation, final blending and lubrication, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for the manufacture of at least three production-scale batches of common blend and for the compression and film-coating of at least three production-scale batches of the 50 mg and 100 mg tablets. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches of the 25 mg strength will be performed post authorization.

Control of excipients
The excipients comply with Ph.Eur., USP/NF or in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units, related substances, assay, thickness, identification of titanium dioxide, subdivision of tablets (25 mg and 50 mg strengths), microbiological contamination and water content. Except for water content, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on several pilot-scale and production-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three pilot-scale batches of 25 mg, and five pilot-scale and three full-scale batches of both the 50 mg and 100 mg tablets. The batches were stored at 25°C/60% RH (6-48 months) and 40°C/75% RH (6 months), and packed in PVC-PE-PVdC/Al-blisters and HDPE bottles. The conditions used in the stability studies are according to the ICH stability guideline. Under both storage conditions an increase of water content was observed during storage and at accelerated conditions a slight increase of total impurities. All parameters remain within the specified limits. The drug product was demonstrated to be photostable. The proposed shelf life of 3 years without any special storage requirements is justified.

In-use stability
Stability data have been provided demonstrating that the product packed in HDPE containers remains stable for 2 years following first opening of the container, when stored at 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is collected from milk sourced by healthy animals under the same condition as milk for human consumption. Further, 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Losartankalium Aurobindo 25 mg, 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Losartankalium Aurobindo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cozaar, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Losartan is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Losartankalium Aurobindo 100 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Cozaar 100 mg film-coated tablets (Merck Sharp & Dohme Limited, UK).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver has been granted for the 25 mg and 50 mg strengths, as the following criteria are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile is similar under identical conditions for the additional strengths and the strength of the biobatch.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 110 healthy male subjects, aged 18-43 years. Each subject received a single dose (100 mg) of one of the 2 losartan potassium formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the washout and sampling period were long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters. Losartan may be administered with or without food. The bioequivalence study under fasting conditions is therefore appropriate.

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. Bioequivalence was shown for the parent and metabolite of losartan.

Results
Eight subjects dropped out the study, including 6 subjects who dropped out as they were absent for period-II check-in. One subject was withdrawn before period-II check-in due to positive urinary drug

screening and one subject was withdrawn before dosing due to abnormal pre dose vitals. The samples of the 102 volunteers who completed the study were analysed.

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

Treatment N=102	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1247 (±490)	1285 (±498)	864 (± 472)	1(±0.8)	1.8(±0.6)
Reference	1272 (±496)	1308 (±500)	931(±431)	0.83 (±0.7)	1.8(±0.6)
***Ratio (90% CI)**	0.98 (0.95-1.01)	0.98 (0.96-1.01)	0.90 (0.82-0.99)	--	--
CV (%)	12	11	40	--	--

$AUC_{0-\infty}$ 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*

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

Treatment N=102	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4320 (±1425)	4514 (±1441)	807 (± 298)	2.5 (±0.9)	3.8(±0.8)
Reference	4455 (±1505)	4661 (±1514)	827(±296)	2.5 (±1.0)	4.0(±0.9)
***Ratio (90% CI)**	97 (95-100)	97(95-99)	98 (95-101)	-	-
CV (%)	10	10	13	-	-

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of losartan under fasted conditions, supported by those of the metabolite losartan carboxylic acid, are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence study sartankalium Aurobindo 100 mg is considered bioequivalent with Cozaar 100 mg film-coated 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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Losartankalium Aurobindo.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hyperkalaemia Hypotension Foetotoxicity
Important potential risks	Elevation of liver function values Renal impairment Hypersensitivity reactions incl. angioedema Decrease in haemoglobin and/or hematocrit
Missing information	Use in children < 6 years Exposure during breast feeding

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cozaar. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. A bridging statement was provided, referring to the successfully user tested PL for another Losartankalium Aurobindo product (authorised through MRP UK/H/1167/001-003). Moreover, the PL text is in line with the harmonised PIL of Cozaar. The bridging report is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Losartankalium Aurobindo 25 mg, 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cozaar film-coated 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 Board followed the advice of the assessors. In the Netherlands marketing authorisation for Lozartankalium Aurobindo was granted on 6 September 2010.

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 Losartankalium Aurobindo with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 30 September 2014.

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