CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Losartan Kalium Jubilant 25 mg, 50 mg and 100 mg film-coated tablets
Jubilant Pharmaceuticals N.V., Belgium

losartan (as potassium)

EU-procedure number: NL/H/2050/001-003/MR
Registration number in the Netherlands: RVG103651,103657,103659

25 February 2011

Pharmacotherapeutic group:	angiotenson II antagonists, plain
ATC code:	C09CA01
Route of administration:	oral
Therapeutic indication:	essential hypertension in adults, children and adolescents aged 6-18 years old; renal disease in adult 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; 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:	5 March 2010
Concerned Member States:	Mutual recognition procedure with DE, DK, PL, and SE
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 Losartan Kalium Jubilant 25 mg, 50 mg and 100 mg film-coated tablets, from Jubilant Pharmaceuticals N.V. The date of authorisation was on 5 March 2010 in the Netherlands. The product is indicated for:

- Treatment of essential hypertension in adults, children and adolescents aged 6-18 years old.
- 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 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 25 mg film-coated tablets (NL license RVG 17617) which has been registered in the UK by Merck Sharp & Dohme Limited since 1994 (original product).
The reference products in the Netherlands are Cozaar 50 mg (NL license RVG 17617) and Cozaar 100 mg (NL license RVG 26791), authorised through the MRP procedure NL/H/1457/002-002/MR.
The innovator of the 25 mg strength is not registered in the Netherlands. For this strength, the MAH refers to a European Reference Product, namely Cozaar 25 mg film-coated tablets which is registered in the UK.

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Cozaar 50 mg film-coated 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. 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.

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 generic medicinal products.

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 potassium, an established active substance described In the USP* and Ph.Eur.*. The active substance is freely soluble in water, sparingly soluble in isopropyl alcohol and slightly soluble in acetonitrile. The substance is polymorph and has been identified as form I.

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
Losartan potassium is manufactured in four steps. The manufacturing process has been adequately described and the active substance has been adequately characterized. No class one solvents were used.

Quality control of drug substance
The drug substance specification and test methods are established in-house by the ASM-holder and adopted by the MAH with additional requirements for particle size. The specification is in line with the Ph.Eur. monograph with additional requirements for residual solvents, azide, Bromo-CMB, BCFI and polymorphic purity. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were adequately stored. A slight but not significant increase of the water content was noted at both storage conditions. The proposed re-test period of 30 months with no special storage conditions was granted.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition

Losartan Kalium Jubilant 25 mg – are are white to off-white, oval shaped, film-coated tablets, debossed with "*J*" on one side and "*25*" on the other side.
Losartan Kalium Jubilant 50 mg – are white to off-white, oval shaped, film-coated tablets, scored on one side, debossed with "*J*" on scored side and "*50*" on the other side. The tablets can be divided into equal halves.
Losartan Kalium Jubilant 100 mg – white to off-white, capsule shaped, film-coated tablets, debossed with "*J*" on one side and "*100*" on the other side.

The excipients are
Tablet core: lactose monohydrate, microcrystalline cellulose (E460), pregelatinised maize starch, magnesium stearate (E572).
Film-coating: hypromellose (E464), hydroxypropylcellulose (E463), titanium dioxide (E171)

The film-coated tablets are packed in blisters (Al/PVC/PE/PVDC).The excipients and packaging are usual for this type of dosage form. The three strengths are manufactured dose proportionally.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to create a film-coated tablet which would be safe efficacious and bioequivalent to the innovator product Cozaar. Comparative dissolution profiles were provided. The choices of the packaging and manufacturing process are justified. The composition and manufacturing process of the batch used in the bioequivalence study is being described in the development. The pharmaceutical development of the product has been adequately performed.

Container closure system
Primary packaging is a blister consisting of a white opaque PVC film laminated with PE film, which is coated with PVdC (triplex film) and a plain aluminium foil coated with heat sellable lacquer. This material was selected based on the packaging materials used for the innovator products.
In the dossier a packing material for bulk shipment is also used. The stability of bulk product was demonstrated, the product was stored at 25°C/60%RH for a period of 6 months. The bulk product is stored in a polyethylene bag, inside a foil based triple laminated bag which is packed inside a HPDE drum.

Manufacturing process
The tablets are manufactured by means mixing of drug substance with excipients, granulation, mixing, compression of tablets and finally, film coating the tablets.The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for two pilot scaled batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorization.

Excipients
The excipients comply with the specifications of the Ph.Eur., with additionally functionally-related tests included. These specifications are acceptable.

Breakability
The 50 mg tablets have a score-line, they were tested for breakability. Results showed compliance with the specification (not more than 1 individual mass is outside the limits of 85 % to 115% of the average mass). Pharmacokinetic parameters such as absorption, distribution, biotransformation, elimination were also studied and summarized.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The tablets comply with the criteria of test A, category 3 of Microbiological quality of pharmaceutical preparations (Ph.Eur. 5.1.4). The product is not intended to be microbiological sterile.

Quality control of drug product
The product specification includes tests for appearance, identification of losartan potassium and titanium dioxide, hardness, water content, disintegration, uniformity of dosage units (mass variation), dissolution, related substances, assay and microbial limits. Release and end of shelf-life specifications are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot scaled batches of each strength, demonstrating compliance with the release specification. A commitment to provided additional batch data of commercial scale batches is made.

Stability of drug product
Stability data on the product has been provided for two pilot scaled batches of the 25 mg, 50 mg and 100 mg product stored at 25°C/60%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC blisters and a polyethylene bag in a foil based triple laminiated bag in a HDPE container for bulk shipment. Results stayed within limits although a slight increase of the water content under all conditions was seen for the blister pack. The shelf-life of 24 months without further storage conditions was granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is prepared from milk and calf rennet. All the excipients have been declared to be without risk of TSE/BSE contamination.

Several commitments have been made by the MAH with regard to quality. Please see page 9 for an overview of these commitments.

II.2 Non clinical aspects

This product is a generic formulation of Cozaar film-coated 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 one bioequivalence study in which the pharmacokinetic profile of the test product Losartan Kalium Jubilant 50 mg film-coated tablets (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Cozaar 50 mg film-coated tablets, (MSD, UK).

The choice of the reference product
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 or with the EU reference product.

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

Bioequivalence study
A open label, randomized, two period, two treatment, two sequence, crossover, balanced single dose, comparative evaluation bioequivalence study was carried out under fasted conditions in 90 healthy male volunteers, aged 18-43 years. Each subject received a single dose (50 mg) of one of the 2 losartan formulations. A randomisation scheme was provided. The tablet was orally administered with 240 ml water after after an overnight fast of 10 hours. The volunteers received a light meal 4 hours upon dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of the products.
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 taken without reference to food intake. 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 first 86 volunteers were included in the study and completed the study as planned.

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 = 86	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	503 ± 248	514 ± 254	231 ± 133	1.25 (0.5 - 4.5)	2.4 ± 1.5
Reference	517 ± 245	528 ± 249	244± 120	1.25 (0.5 - 4.5)	2.4 ± 1.2
***Ratio (90% CI)**	0.96 0.93– 1.00	0.97 0.93 – 1.00	0.92 0.83 – 1.02	---	---
CV (%)	15	15	42	---	---

$AUC_{0-\infty}$	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*

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 Losartan Kalium Jubilant 50 mg film-coated tablets and Cozaar 50 mg film-coated tablets 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
In the clinical study report an overview of the pharmacokinetics of losartan is given, in which waiving of bioequivalence studies with the 25 and 100 mg formulation is discussed briefly. Only the linearity of the pharmacokinetics of losartan and its main metabolite are discussed.
From the quality part of the dossier it was clear the products are fully dose proportional. The dissolution profiles of test product 50 mg vs NL reference product (Cozaar 50 mg), and test product 100 mg vs NL reference product (Cozaar 100) are provided. Therefore, a biowaiver can be granted for the 25 and 100 mg.

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
The SPC has been harmonised with the SPC of Cozaar. The Committee for Medicinal Products for Human Use (CHMP) finalised the referral by consensus under Article 30 of Directive 2001/83/EC recommending the harmonisation of the product information across the European Union for Cozaar 12.5mg, 25 mg, 50 mg and 100 mg filmcoated tablets in April 2008.
Furthermore, the Pharmacovigilance Working Party has agreed a wording in October 2008, regarding the use of Angiotensin II Receptor Antagonists (AIIRAs) during pregnancy and lactation. The SPC has been aligned to the Article 30 outcome of Cozaar and the wording as agreed in the PhVWP.

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.
There were 17 questions about the content and they address the key safety issues. The questions cover the areas *locate information in the package leaflet*, *understand it* and *know how to act on it*. In the test report five scoring categories were used for traceability and understanding: straightforward, basic, modest, difficult and very difficult.
After a pilot test with 2 subjects, two rounds with 10 subjects were undertaken. They were spread on age, sex and education quotas. Given the nature of this medicine and its use for treatment of high blood and

diabetes, the age demographics for this user test were skewed toward an older population as the elder demographic is most likely to be using this medicine, this is acceptable. Recruitment took place via online advertisements and/or local press. The participants selected for this test were disqualified if they ever had been involved in a user test before or if they work or had worked in the following industries: Pharmaceuticals, Medical, Market research or Media.
The test took between 15 and 31 minutes. The interviews were held by one out of two interviewers.
Four solicited questions were asked to complete the questionnaire with regards to positive, negative and stylistic feedback about the readability of the PIL, in addition to a rating scale question. The answers to these questions are included in the report. On a scale of 1 (very easy) to 5 (very difficult) 6 participants gave the leaflet a 1, 10 participants a 2, 4 participants a 3 and 2 participants a 4. The positive feedback was in general that the leaflet was clear and has a good lay out and the negative feedback that it contains a lot of information especially side effects.
In the first round all questions were answered correctly. There was one participant who answered incorrectly to the question where he found the information to question 11. But as all questions were answered correctly and as no conclusive trends could be found across testing where participants failed to locate or understand a given point but were rather only isolated incidents, there were no suggestions for revision to the PIL based on the first round of testing.
In the second round again all questions were answered correctly. In this round one participant answered incorrectly to the question where he found the answer to question 5. Furthermore, one participant took several pauses while scanning Section 4 before finding and understanding the correct information regarding question 8.
In both rounds at least 90% of the participants were able to find the correct information in the package leaflet and 100% of participants were able to answer the questions correctly. The user test is found to be acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Losartan Kalium Jubilant 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Cozaar 50 mg and 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, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Losartan Kalium Jubilant 25 mg, 50 mg and 100 mg film-coated tablets are authorised in the Netherlands on 5 March 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 Losartan Kalium Jubilant 25 mg, 50 mg and 100 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 21 October 2010.

A European harmonised birth date has been allocated 2 September 1994 and subsequently the first data lock point for losartan is September 2010. Therefore the first PSUR will be submitted 60 days after Data Lock Point of September 2010. The second PSUR will be used to support the renewal application.

The date for the first renewal will be 31 May 2014

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

<u>Quality - medicinal product</u>
- The MAH has committed to submit the results of a third validation batch when the batch is executed.
- The MAH has committed to validate the first three full-scale consecutive commercial batches as per the protocols.
- The MAH committed to perform stability studies on three industrial size batches.
- The MAH has committed to subject the first three commercial batches of the additional batch sizes to process validation.
- the MAH has committed to determine the shelf-life of the finished product in its final package in accordance with EMEA's "*Note for Guidance on Start of Shelf-life of the Finished Dosage Format*".

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BCFI	2-butyl-4-chloro-5-forrmylimidazole
BP	British Pharmacopoeia
Bromo-CFB	2-cyano4'-bromomethyl biphenyl
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