CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Losartankalium/HCT 50/12.5 mg Jubilant and 100/25 mg Jubilant film-coated tablets
Jubilant Pharmaceuticals N.V., Belgium

losartan (as potassium) / hydrochlorothiazide

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/2037/001-002/MR
Registration number in the Netherlands: RVG 104738-9

20 January 2011

Pharmacotherapeutic group:	Angiotensin II antagonists and diuretics
ATC code:	C09DA01
Route of administration:	oral
Therapeutic indication:	essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.
Prescription status:	prescription only
Date of first authorisation in NL:	29 January 2010
Concerned Member States:	Mutual recognition procedure with DE, DK, SE, and 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 Losartankalium/HCT 50/12.5 mg Jubilant and 100/25 mg Jubilant film-coated tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 29 January 2010 in the Netherlands. The product is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

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

Losartan
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.

HCTZ
Hydrochlorothiazide is a thiazide diuretic which acts by inhibiting fluid-expelling and blood pressure-lowering agents which increase the tubular re-absorption of sodium in the cortical diluting segment. It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

The components of the Kaliumlosartan + HCTZ Alet film-coated tablets have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components.
Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cozaar-Comp 50/12.5 mg and 100/25 mg film-coated tablets (NL license RVG 103694 and 105053) which has been registered in the UK by Merck Sharp & Dohme Limited since 1996 (original product). The reference products in the Netherlands are Hyzaar 50/12.5 mg and Fortzaar 100/25 mg film-coated tablets, registered since 1996 (NL license RVG 19269) and 1999 (NL license RVG 23597) respectively, authorised through the MRP (NL/H/1458/001-002/MR).

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 Comp 100/25 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 substances

1- Losartan potassium

General information
Losartan potassium is an established active substance which is described in the European Pharmacopoeia (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 this 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 ASMF-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 retest period of 3 years with no special storage conditions are justified.

2- Hydrochlorothiazide

General information
Hydrochlorothiazide is an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is very slightly soluble in water. No evidence of polymorphism has been reported for hydrochlorothiazide.

The CEP procedure is used for this 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 suitablity 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacturing process
The manufacturing process is covered by the CEP.

Quality control of drug substance
The MAH's drug substance specification is in line with the CEP, with additional requirements for residual solvents and impurities. The specifications are in line with the Ph.Eur. monograph. Batch analytical data demonstrating compliance with the drug substance specification have been provided on 1 full-scale batch.

Stability of drug substance
The active substance from is stable for 5 years if stored under the proposed 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
Losartan Potassium/HCT 50/12,5 mg Jubilant – are yellow, oval shaped, film-coated tablets, debossed with "*J*" on one side and "*50+*" on the other.
Losartan Potassium/HCT 100/25 mg Jubilant – are yellow, oval shaped, film-coated tablets, debossed with "*J*" on one side and "*100+*" on the other.

For marketing the drug product is packed in Al/Al-blister packaging.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), pregelatinised maize starch, magnesium stearate (E572).
Film-coating - titanium dioxide (E171), hypromellose 6cP (E464), hydroxypropylcellulose (E463), quinoline yellow (E104) aluminium lake.

The excipients and packaging are usual for this type of dosage form. The formulations of the 50/12.5 mg tablets and 100/25 mg 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 main development studies were the characterisation of the originator product, dissolution method development formulation development, *in vitro* studies and the manufacturing process

development. The batch of drug product used for the BE studies was manufactured according to the finalized formulation. The pharmaceutical development of the product has been adequately performed.

Container closure system
For the drug product, Al-Al cold form blisters consisting of a multilayer cold form, aluminium based blister film as forming material and 25 micron hard tempered aluminium foil as lidding are used. This is a commonly used packaging material.

Manufacturing process
The main steps of the manufacturing process are the mixing of drug substance and excipients, granulation, mixing, compression into tablets and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches per strength. The product is manufactured using conventional manufacturing techniques.
The MAH has committed to subject the third pilot scale batch (for each strength) to prospective validation as per the process validation protocol. Also the first 3 consecutive commercial batches of both strengths will be subjected to prospective validation. Results from validation studies should be available on request.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, water content, uniformity of dosage units, dissolution, related substances, assay and microbial limits. Except for assay and water content, the release and shelf-life limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches per strength, demonstrating compliance with the release specification.

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 drug product complies with test A of category 3 of the Ph.Eur. monograph on Microbiological Quality of Pharmaceutical Preparations (5.1.4). This is acceptable for tablets.

Stability of drug product
Stability data on the product have been provided two pilot-scale batches 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 Al/Al-blisters. No changes are observed under both conditions. The proposed shelf-life of 24 months for the product when stored in the original package in order to protect from moisture is justified.
The MAH has committed to perform a post approval stability study on the first 3 production batches of the drug product on long term studies for the duration of the proposed shelf-life and on accelerated studies for 6 months, according to the stability protocol. The ongoing real time stability studies on submission batches will be continued for the duration of the proposed shelf-life. The results of the ongoing stability studies throughout the proposed shelf-life are awaited as soon as available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose monohydrate a TSE certificate has 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.

II.2 Non clinical aspects

This product is a generic formulation of Cozaar-Comp, 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 losartan or hydrochlorothiazide 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 and hydrochlorothiazide are both well-known active substances 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 Losartankalium/HCT 100/25 mg Jubilant film-coated tablets (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Cozaar Comp 100/25 mg film-coated tablets (Merck Sharp & Dohme Limited, 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 (if applicable) in different member states.

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

Bioequivalence study
A open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 94 healthy Asian male volunteers, aged 18-44 years. Of the subjects, four were not dosed as they were reserves. Each subject received a single dose (100 mg losartan, 25 mg hydrochlorothiazide) of one of the 2 losartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water under fasting conditions. There was a wash-out period of 13 days between treatments.

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, 48.0 and 72.0 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 and hydrochlorothiazide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of losartan and hydrochlorothiazide. 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.

The data of the main metabolite of losartan, losartan carboxy acid, were considered supportive.

Results
Of the 90 dosed subjects, 77 completed the study. The thirteen subjects who did not complete the study, discontinued due to the following reasons: during dosing period I, four subjects were discontinued on the basis of medical grounds after dosing (vomiting, 2 test, 2 reference) and one subject did not report to the

testing facility to give the post dose blood samples (t=36, t=48, t=72). At the beginning of dosing period II, one subject was discontinued due to protocol violation, as the subject tested positive in the urine scan for drugs of abuse, discontinuation according to protocol. One subject did not report to the facility for period II dosing. During period II, five subjects were discontinued on the basis of medical grounds (two before dosing; fever, both reference and three after dosing; vomiting and/ or giddiness, two test and one reference) and one subject did not report to the testing facility to give the post dose blood samples (t=36, t=48, t=72). All 77 subjects who completed the study where included in PK- and statistical analysis.

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

Treatment N = 77	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1196 ± 547	1207 ± 552	668 ± 342	1.5 ± 0.87	2.5 ± 1.2
Reference	1213 ± 571	1227 ± 583	692 ± 357	1.7 ± 0.93	2.7 ± 1.5
***Ratio (90% CI)**	0.99 (0.97-1.02)	0.99 (0.96-1.02)	1.00 (0.91-1.10)	---	---
CV (%)	10.1	10.0	36.8	---	---

$AUC_{0-\infty}$ 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 carboxy acid under fasted conditions.

Treatment N = 77	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6570 ± 2039	6612 ± 2044	1006 ± 362	3.3 ± 1.0	7.0 ± 1.6
Reference	6560 ± 1949	6604 ± 1956	995 ± 352	3.4 ± 1.0	7.1 ± 1.9
***Ratio (90% CI)**	1.00	1.00	1.01	---	---
CV (%)	6.2	6.2	12.9	---	---

$AUC_{0-\infty}$ 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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N = 77	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1059 ± 324	1074 ± 330	128 ± 37.6	3.0 ± 1.0	9.6 ± 1.5
Reference	1047 ± 285	1058 ± 287	130 ± 41	3.1 ± 1.0	9.5 ± 1.4
*Ratio (90% CI)	1.01 (0.97-1.05)	1.01 (0.97-1.05)	0.99 (0.94-1.04)	---	---
CV (%)	13.8	14.5	18.7	---	---

$AUC_{0-\infty}$ 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*

Bioequivalence has been shown, as the 90% confidence intervals of the losartan, and hydrochlorothiazide pharmacokinetic parameters are within the 90% CI acceptance criteria of 0.80-1.25. The extrapolated area of the AUC is never higher than 20% and t_{max} was not observed in the first sample time. The C_{max} for losartan and losartan acid was out of the validated range in a few subjects, but a dilution integrity experiment has been successfully performed. The MAH also provided complete statistics of losartan acid.

Based on the submitted bioequivalence study, it can be concluded that Losartankalium/HCT 100/25 mg Jubilant film-coated tablets and Cozaar Comp 100/25 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
A request for a biowaiver was made to extrapolate the results of the study with the 100/25 mg strength to the 50/12,5 mg strength. The MAH showed that all requirements were fulfilled:

a. Pharmacokinetics for hydrochlorothiazide and Losartan is linear over the dose range in question.
b. The manufacturing process and manufacturing site for the 50/12.5 mg tablets and 100/25 mg tablets are identical.
c. The formulations of the 50/12.5 mg tablets and 100/25 mg tablets are dose proportional.

The *in-vitro* dissolution profiles of the 50/12.5 mg tablets and 100/25 mg tablets are similar. Therefore biowaiver for the 50/12.5 mg strength was granted.

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
In view of the existing knowledge and experience with both active substances losartan and hydrochlorothiazide, the available data and the known risk benefit profile it is accepted that the MAH will perform the standard pharmacovigilance activities as described in volume 9 of The rules governing medicinal products in the European Union.
An additional Risk Management Plan and Risk Minimisation Plan are not required at the moment.

Product information

SPC
The SPC has been harmonised with the SPC of Cozaar Comp. Cozaar Comp is the collective name for Hyzaar, Fortzaar and Cozaar Plus (procedure NL/H/1458/001-003) with the active substances losartan and hydrochlorothiazide. For Cozaar Comp, an article 30 procedure has been finalised in September 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 Comp 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. The content of the package leaflet is harmonised with that of the innovator Cozaar Comp.
The composition of the subject population is acceptable as far as age, gender and education are concerned. Eighteen questions were prepared to test for findability, understandability and applicability. The test consisted of a preliminary round of testing with 2 participants, followed by two rounds of testing with 10 participants each.

The results of the first round of testing met the study objectives. Therefore, no amendments to the package leaflet were considered necessary. Also the results of the second round of testing met the study objectives.
In addition to the questionnaire, there were four questions at the end of the test with regards to positive, negative and stylistic feedback about the readability of the PL. The participants were also asked to rate the leaflet as a whole using a scale form. Ten participants commented on the length of the PL as a negative aspect. However, given the complexity of this medicine and the need to accurately represent its SPC, it cannot be shortened without losing some of the key safety messages of the medicine, according to the company. Therefore, from the subject's answers to these questions and general comments, no adaptation of the package leaflet was possible or deemed necessary.
There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Losartankalium/HCT 50/12.5 mg Jubilant and 100/25 mg Jubilant film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cozaar Comp 50/12.5 mg and 100/25 mg film-coated tablets. Cozaar Comp 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. Losartankalium/HCT 50/12.5 mg Jubilant and 100/25 mg Jubilant film-coated tablets are authorised in the Netherlands on 29 January 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/HCT 50/12.5 mg Jubilant and 100/25 mg Jubilant 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 15 February 1995 and subsequently the first data lock point for losartan/hydrochlorothiazide is February 2013. Therefore the first PSUR will be submitted 60 days after Data Lock Point February 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be 31 October 2013.

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

Quality - medicinal product

- The MAH has committed to subject the third pilot scale batch of a certain size per strength to prospective validation as per the process validation protocol. Also the first 3 consecutive commercial batches of both strengths will be subjected to prospective validation. Results from validation studies should be available on request.
- The MAH has committed to perform a post approval stability study on the first 3 production batches of the drug product on long term studies for the duration of the proposed shelf-life and on accelerated studies for 6 months, according to the stability protocol. The ongoing real time stability studies on submission batches will be continued for the duration of the proposed shelf-life. The results of the ongoing stability studies throughout the proposed shelf-life are awaited as soon as available.

List of abbreviations

AIIRAs	Angiotensin II Receptor Antagonists
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
DM water	Demineralised water
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