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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kaliumlosartan/Hydrochlorothiazide HCS 50/12,5 mg and 100/25 mg, film-coated tablets HCS bvba, 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/1947/001-002/MR
Registration number in the Netherlands: RVG 32759,32760

9 November 2010

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:	11 May 2009
Concerned Member States:	Mutual recognition procedure with CZ, EL, ES, FR, HU, PL, SI, SK
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 Kaliumlosartan/Hydrochlorothiazide HCS 50/12,5 mg and 100/25 mg film-coated tablets from HCS bvba, Belgium. The date of authorisation was on 11 May 2009 in the Netherlands. The product is indicated for in the treatment of essential hypertension in patients whose blood pressure has not been adequately controlled by 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 as by inhibiting fluid-expelling and blood pressure-lowering agent 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 axcount 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 products Hyzaar 50 mg/12.5 mg (NL license RVG 19269) and Fortzaar 100 mg/25 mg (NL license RVG 23597), which have been registered in the Netherlands by Merck, Sharpe & Dome B.V. since 1996 and 1999, respectively (original product). In addition, reference is made to Cozaar Comp 100mg/25 mg film-coated tablets, authorised since 1996 in Denmark (reference product).
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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Lorzaar Plus, registered in Germany. Another

bioequivalence study was submitted during the MRP, in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Fortzaar 100/25 mg tablets, registered in the Netherlands. 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 a paediatric development programme is not required for generics.

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 drug products at issue include two active substances. The first active substance is Losartan potassium, a well-known substance, which is described in the USP*. The drug substance is a white to almost white crystalline powder which is freely soluble in ethanol and slightly soluble in 0.1 M hydrochloric acid. Six polymorphic forms are known.
The second active substance, hydrochlorothiazide, is described in the Ph.Eur.*. It is a white to almost white crystalline powder, which is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol and it dissolves in dilute solutions of alkali hydroxides.

The Active Substance Master File (ASMF) procedure is used for losartan potassium. 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

The CEP procedure is used for hydrochlorothiazide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

<u>Manufacture</u>
The manufacture of losartan potassium consists of two main steps: synthesis of losartan and formation of the potassium salt. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material and solvents.

<u>Quality control drug substance</u>
The drug substances specifications are in line with resp. the DMF and the CEPs. For both substances is the specification acceptable in view of the route of synthesis and the various European guidelines. Requirements on particle size are not part of a CEP, but the particle size distribution of the specification for the drug substances (losartan potassium ánd hydrochlorothiazide) is in accordance with the particle size of the drug substances in the biobatch.

Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
Losartan potassium
Stability data on the active substance have been provided for three full-scaled batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Moreover, stability data for three pilot-scaled batches, stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months), have been provided. The batches were stored in the proposed commercial packaging.
No trends have been observed at both conditions. The proposed re-test period of 36 months without special storage conditions is justified.

Hydrochlorothiazide from one manufacturer
The active substance is stable for four years when adequately stored. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrohclorothiazide from another manufacturer
The active substance is stable for five years when adequately stored. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *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
The products are formulated as film-coated tablets which are packaged in PVC/PVDC//Al blisters.

Losartan potassium/Hydrochlorothiazide HCS 50/12.5 mg are yellow, oval, moderately biconvex, film-coated tablets with one-sided halving score, tablet dimension 6 mm x 12 mm (oval shape) thickness 3.8 – 4.7 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Losartan potassium/Hydrochlorothiazide HCS 100/25 mg are yellow, oval, slightly biconvex, film-coated tablets.

The excipients are:
Tablet core: maize starch, pregelatinised, microcrystalline cellulose, lactose monohydrate, magnesium stearate.
Film-coating: hypromellose, macrogol 4000, quinoline yellow (E104), talc, titanium dioxide (E171).

The excipients and packaging are usual for this type of dosage form.
The two dosages are completely dose proportional

Pharmaceutical development
The development of the product has been described, the choice of excipients is acceptable. The wet granulating process, with water as granulating liquid, was chosen on the basis of data that were obtained in different experiments. The packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
Losartan potassium, and part of the starch and the lactose are sieved and mixed. Purified water is added as granulating liquid to obtain wetted mass. The wetted mass is granulated. The granulated mass is dried and sieved. The dry granulate is mixed with hydrochlorothiazide, cellulose and the other part of the starch and the lactose. Magnesium stearate is added to the mixture and mixed. Compressing takes place. A coating suspension is prepared and the cores are coated by continuous spraying of the coating suspension. After spraying, the film coated tablets are kept rotating and dried. The film coated tablets are packed.

The manufacturing process has been sufficiently validated. The product is manufactured using conventional manufacturing techniques.

Excipients
All excipients, except for quinoline yellow, comply with the Ph. Eur. All specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of losartan, potassium, hydrochlorothiazide, quinoline yellow and titanium dioxide, uniformity of mass, disintegration, dissolution of losartan potassium and hydrochlorothiazide, assay of losartan potassium and hydrochlorothiazide, related substances, water, hardness and microbiological purity. The release and shelf-life limits are identical, except for total impurities and assay of hydrochlorothiazide. The specifications are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data have been provided for two production scaled batches and two pilot scaled batches of the 50/12.5 mg tablets and for one production scaled batch and three pilot scaled batches of the 100/25 mg tablets. Compliance with the release requirements has been demonstrated.

Stability tests on the finished product
50/12.5 mg strength
Stability data on the product have been provided three pilot-scaled and three production scaled-batches. The pilot batches are stored at 25°C/60% RH (60 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months). A full-scale batch is stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months); two other production batches (24% of maximum full-scale) are stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline except for the intermediate conditions for the pilot batches. No objection has been made. The batches were stored in Al/PVC-PVDC blister.
Changes for impurities are seen after storage at accelerated conditions. A mass-imbalance is observed after storage at intermediate conditions for the pilot batches. However, this is not observed for the three production batches. Therefore, the proposed shelf-life of 5 years if stored below 30°C is justified.

100/25 mg strength
Stability data on the product have been provided for two pilot-scaled and one production scaled batches. The pilot batches are stored at 25°C/60% RH (48 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months). The full-scale batch is stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline except for the intermediate conditions for the pilot batches. No objection has been made. The batches were stored in Al/PVC-PVDC blister.
Changes for impurities are seen after storage at accelerated conditions. The proposed shelf-life if 4 years if stored below 30°C is justified.

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.

II.2 Non clinical aspects

These products are generic formulations of Fortzaar and Hyzaar, which are 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 and 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 potassium and hydrochlorthiazide are a well-known active substances with established efficacy and tolerability. The use of the combination is also well established.

For this generic application, the MAH has submitted one bioequivalence study during the national phase of the registration in the Netherlands, and a second bioequivalence study during the Mutual Recognition Procedure following the comments from one of the Concerned Member States.
The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Losartan and hydrochlorothiazide may be administered with or without food. 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 choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of qualitative compositions of the Dutch and German reference products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. Dissolution tests with the test product and the German reference product (Lorzaar Plus tablets) have been provided.

Bioequivalence study with 50 mg/12.5 mg strength
In this study the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Lorzaar Plus 50 mg/12.5 mg film-coated tablets, registered by MSD in Germany.

A single dose, crossover, bioequivalence study was carried out under fasting conditions in 35 healthy male volunteers (aged 18 – 32 years). Each subject received a single dose (50 mg/12.5 mg) of one of the 2 losartan / hydrochlorothiazide formulations.. The products were administered with 180 ml water. Between the treatments the washout period was 7 days.

Blood samples to determine the valsartan concentrations were taken pre-dose dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 and 36 hours after dosing. Plasma samples were anlaysed for losartan, the active metabolite losartan carboxy acid and hydrochlorothiazide. The data of the metabolite, losartan carboxy acid, were considered supportive.

Results
A total of 34 subjects completed the study. On day 1, before the start of the first treatment one volunteer was excluded due to health problems. Of one subject only analytical data for losartan and losartan carboxy acid was available of the first treatment period. Thirty-three subjects were eligible for pharmakonietic analysis.

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

Treatment N=33	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	458 ± 120	496 ± 141	252 ± 96	1.0 (0.5-2.0)	3.1 ± 3.0
Reference	472 ± 164	512 ± 174	253 ± 104	1.0 (0.5-2.5)	3.2 ± 3.0
***Ratio (90% CI)**	0.99 (0.92-1.06)	0.98 (0.91-1.06)	1.01 (0.86-1.18)	--	--
CV (%)	18	19	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 1B. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) of losartan carboxy acid under fasted conditions.

Treatment N=33	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	2411 ± 697	2448 ± 694	320 ± 104	3.5 (2.0-6.0)	4.6 ± 0.8
Reference	2448 ± 694	2572 ± 697	312 ± 100	4.0 (2.0-5.0)	4.7 ± 0.9
***Ratio (90% CI)**	0.99 (0.95-1.04)	0.99 (0.96-1.03)	1.03 (0.97-1.09)	--	--
CV (%)	10.9	8.5	13.7	--	--

$AUC_{0-\infty}$ 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*

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

Treatment N=34	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h	$T_{1/2}$ h
Test	474 ± 144	507 ± 147	81 ± 25	2.0 (1.0-3.5)	6.9 ± 1.3
Reference	478 ± 135	512 ± 134	78 ± 21	2.0 (1.0-3.0)	7.2 ± 1.7
***Ratio (90% CI)**	0.98 (0.93-1.04)	0.98 (0.93-1.03)	1.03 (0.93-1.13)	--	--

CV (%)	14.7	13.1	24.3	--	--

$AUC_{0-\infty}$ 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 for AUC_{0-t}, and C_{max} of losartan, losartan carboxy acid and hydrochlorothiazide are 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, losartan carboxy acid and hydrochlorothiazide it can be concluded that the reference and test tablets are bioequivalent with respect to rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

According to one of the Concerned Member States the analytical method was not adequately validated and therefore not acceptable for analysis of the plasma samples. Therefore, the MAH has submitted a second bioequivalence study to solve this issue.

Bioequivalence study with 100 mg/25 mg strength
In this study the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Fortzaar 100 mg/25 mg film-coated tablets, registered by MSD in the Netherlands.

A single dose, crossover, bioequivalence study was carried out under fasting condition in 60 healthy adult male volunteers (aged 23-55 years). Each subject received a single dose (100 mg/25 mg) of one of the 2 losartan / hydrochlorothiazide formulations. The products were administered with 240 ml water. Between the treatments the washout period was 14 days.

Blood samples to determine the valsartan concentrations were taken pre-dose dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours after dosing. Plasma samples were anlaysed for losartan, the active metabolite losartan carboxy acid and hydrochlorothiazide

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples.

Results
Two subjects (no 31 and 59) did not show up for period 2 check-in. A total of 58 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=58	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	763 ± 245	772 ± 248	448 ± 190	1.3 (0.5-2.5)	2.1 ± 0.6
Reference	774 ± 237	783 ± 238	246 ± 50	1.3 (0.5-2.5)	2.1 ± 0.6
***Ratio (90% CI)**	0.98 (0.94-1.02)	0.98 (0.95-1.02)	0.93 (0.84-1.03)	--	--
CV (%)	12.0	11.8	32.8	--	--

$AUC_{0-\infty}$	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

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

Treatment N=58	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	3991 ± 1202	4060 ± 1209	692 ± 251	2.5 (1.7-5.0)	5.0 ± 1.1
Reference	3949 ± 1253	4018 ± 1256	690 ± 255	2.5 (1.7-5.0)	4.9 ± 0.9
***Ratio (90% CI)**	1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.01 (0.98-1.05)	--	--
CV (%)	9.4	9.2	11.6	--	--

$AUC_{0-\infty}$	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

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

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	895 ± 170	939 ± 174	137 ± 32	2.0 (1.3-5.0)	8.7 ± 1.1
Reference	908 ± 197	955 ± 203	132 ± 34	2.5 (1.0-4.0)	8.7 ± 1.0
***Ratio (90% CI)**	0.99 (0.99-1.03)	0.99 (0.96-1.02)	1.04 (0.99-1.10)	--	--
CV (%)	11.5	11.1	11.6	--	--

$AUC_{0-\infty}$	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

The 90% confidence intervals for AUC_{0-t}, and C_{max} of losartan, losartan carboxy acid and hydrochlorothiazide are 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, losartan carboxy acid and hydrochlorothiazide it can be concluded that the reference and test 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

The losartan-hydrochlorothiazide 50 mg/12.5 mg tablets are completely dose proportional with the losartan-hydrochlorothiazide 100 mg/25 mg tablets. The MAH sufficiently supported that the pharmacokinetics of losartan and hydrochlorothiazide are linear in the relevant dose range. Also the manufacturing process and the manufacturing site are the same for both strengths. Therefore, the results of the losartan-hydrochlorothiazide 50 mg/12.5 mg tablet may be extrapolated to the losartan-hydrochlorothiazide 100 mg/25 mg tablet and vice versa, because the conditions mentioned in (CPMP/EWP/QWP/1401/98) are fulfilled.

Risk management plan

The combination losartan potassium/hydrochlorothiazide was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile 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

The SPC is in line with the SPC of innovator product which is recently harmonised during a art 30 procedure (25 September 2008) and updated during procedure NL/H/1458/001-002/II/002 to include recommendations for pregnancy and lactation.

Readability test

The MAH submittted a bridging report for the purpose of the User Testing on readability of the package leaflet. The reference product is Losartan/Hydrochlorothiazide KRKA 50 mg/12.5 mg and 100 mg/25 mg film coated tablets (further Losartan/Hydrochlorothiazide KRKA tablets). Results of User Testing on readability of Losartan/Hydrochlorothiazide KRKA tablets were submitted in the registration procedure CZ/H/0101/01/MR. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

Two documents comparing the differences between the two leaflets with differences highlighted and summarised have been submitted as well as the complete readability testing report of Losartan/Hydrochlorothiazide KRKA tablets.

The bridging is justified on the following grounds:

- Both products contain the same active ingredients, losartan potassium and hydrochlorothiazide.
- Both products are licensed for the same indication.
- Both products have the same route of administration.
- The precautions before taking the two products are similar.
- The instructions for taking the products are the same.
- The expected side effects of the two products are the similar.
- The package leaflets have common design and layout.

Besides, the PL for current product was also harmonized with PLL for Cozaar Comp film-coated tablets published as originators Article 30 - 'harmonisation' referral on 25/09/2008 and therefore, actually bridging for lay-out aspects should have been sufficient.

It is concluded that the proposed leaflet is legible, clear and easy to use and does not require additional readability testing. 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.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kaliumlosartan/Hydrochlorothiazide HCS 50/12,5 mg and 100/25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Hyzaar 50 mg/12.5 mg and Fortzaar 100 mg/25 mg tablets. Hyzaar and Fortzaar tablets are well-known medicinal products 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.

The Board followed the advice of the assessors. Kaliumlosartan/Hydrochlorothiazide HCS 50/12,5 mg and 100/25 mg film-coated tablets were authorised in the Netherlands on 11 May 2009.

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/Hydrochlorothiazide HCS film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 17 May 2010.

An European harmonised birth date has been allocated (15 February 1995) and subsequently the first data lock point for losartan-hydrochlorothiazide is February 2013. The first PSUR will cover the period from May 2009 to February 2013, after which the PSUR submission cycle is 3 years. The date for the first renewal will be: October 2013.

There were no post-approval commitments made during the procedure.

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