CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kaliumlosartan + HCTZ Axcount 50 mg/12.5 and 100 mg/25 mg film-coated tablets
Axcount Generika AG, Germany

losartan 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/1434/001-002/MR
Registration number in the Netherlands: RVG 10223,10225

19 October 2009

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:	16 April 2008
Concerned Member States:	Mutual recognition procedure with DE
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 + HCTZ axcount 50 mg/12.5 mg and 100 mg/25 mg film-coated tablets, from Axcount Generika. The date of authorisation was on 17 April 2008 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 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 Hyzaar and Fortzaar authorisations in Germany (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 Fortzaar 100 mg/25 mg, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and 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 substances as well as for the manufacturing and assembly of these products prior to granting its national authorisation.

Active substance
The active substance Losartan potassium is a well-known substance, which is described in the USP*. The drug substance is a white to almost white crystalline powder, and six polymorphic forms are known.
The 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.

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.

Manufacture
Losartan potassium is prepared in a five step synthesis. Class 1 solvents are used in the preparation of the starting material of losartan. Hydrochlorothiazide is prepared in a two step synthesis. The drug substances have been adequately characterized. In general sufficient information has been provided on the syntheses.

Specification
Hydrochlorothiazide specifications are acceptable with regards to residual solvents and related substances. The specifications are acceptable in view of the route of synthesis and the various ICH guidelines and EP monographs. Losartan potassium specifications are also acceptable with regard to residual solvents. Two class one solvents were used in the manufacturing, and were adequately limited and monitored in a starting material. Different spectra of three batches are included in the dossier and show consistency of the polymorphic form. Specifications for the particle sizes of both substances have

been included. Batch analytical data demonstrating compliance with these specifications have been provided for 3 production-scale batches of losartan potassium and 3 production-scale batches of hydrochlorothiazide.

Stability
Stability data of losartan potassium have been obtained during storage at 25ºC/60% RH for up to 24 months. The drug substance was adequately packaged. The drug substance is stable with respect to degradation. Based on the data provided, a re-test period of 24 months be granted. A re-test period of 4 years is noted for hydrochlorothiazide on the CEP, when adequately stored.

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

Medicinal Product

Composition
The products are formulated as film-coated tablets and are packaged in PVC-PE-PVDC/Al blisters. Two strengths are developed: Kaliumlosartan + HCTZ axcount 50mg/12.5 mg tablets and 100mg/25 mg tablets containing 50 mg or 100 mg losartan potassium and 12.5 mg or 25 mg hydrochlorothiazide, respectively.

Kaliumlosartan + HCTZ axcount 50 mg/12.5 mg are white, oblong, biconvex tablets measuring approximately 13.7 × 6.7 mm with a scoreline on both sides. The scoreline is to facilitate breaking for ease of swallowing and not to divide into equal doses.
Kaliumlosartan + HCTZ axcount 100 mg/25 mg are white, oblong, biconvex tablets measuring approximately 15.3 × 6.7 mm with a scoreline on both sides. The tablet can be divided into equal halves.

The excipients are:
Tablet core: microcrystalline cellulose (E460a), lactose monohydrate, pregelatinised maize starch, sodium starch glycolate type A, and magnesium stearate (E572).
Film-coating: hydroxypropyl cellulose (E463), hypromellose 6cP (E464), and titanium dioxide (E171).
The two dosages formulations are completely dose proportional.

Pharmaceutical development
The development of the products is satisfactorily performed and explained. The excipients used are common in the manufacture of film-coated tablets. The packaging is usual and suitable for the products at issue. The efficacy of the score-line has been demonstrated. Dissolution profiles of the drug product and several commercial reference products have been included in the dossier. The breakline is included in order to subdivide the tablets into parts either to ease the intake of the tablets (50 mg/12.5 mg tablets) or to comply with the posology (100 mg/25 mg tablets). The efficacy of the break-marks was assessed on the coated tablets in the validation of the production process.

Excipients
For all excipients, the Ph.Eur. specifications and methods have been adopted, except for Opadry White 20A18334. Opadry White conforms to in-house specifications and to the Ph.Eur./USP or JP specifications of the three ingredients. The specifications and quantitative formula are described in the dossier .

Manufacturing process
The tablets are prepared by a five-step process consisting of sieving and blending of the dry ingredients, tablet compression, coating and packaging.

Product specification
The product specifications for the tablets include tests for appearance, identity (both substances, potassium and titanium dioxide), assay, related substances, water content, uniformity of dosage units, breakability, tablet hardness, disintegration and dissolution. Microbiological quality of the products will be tested on a non-routine basis. The release and shelf-life requirements are identical and most are

acceptable. Batch analysis data have been provided for two pilot scale batches and one laboratory scale batch of both tablet strengths. Compliance with the release requirements has been demonstrated.

Stability tests on the finished product
The tablets have been stored at 25ºC/60% RH, 30 ºC/65% RH and 40ºC/75% RH for up to 36 months. An increase in one degradation product is seen, which resulted in out of specifications under accelerated conditions. A shelf-life of 36 months when stored below 30 ºC can be granted.

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

This product is a generic formulation of Hyzaar and Fortzaar, 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 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 and hydrochlorothiazide are both well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Kaliumlosartan + HCTZ axcount 100 mg/25 mg film-coated tablets (Axcount Generika, Germany) is compared with the pharmacokinetic profile of the French reference product Fortzaar tablets (Merck, Sharp & Dome, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results in different member states (DE, DK, EL, FR, NL, UK) and qualitative compositions of the Dutch and French reference products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

A single dose, randomised, open-label, crossover bioequivalence study was carried out under fasted conditions in 70 healthy volunteers (35 male, 35 female), aged 18-43 years. Each subject received a single dose (one tablet: 100 mg losartan + 25 mg hydrochlorothiazide) of one of the 2 losartan-hydrochlorothiazide formulations. The tablet was orally administered with 200 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 11 days. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.
All 70 subjects were eligible for pharmacokinetic analysis.

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

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.

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

Treatment N=70	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	970 ± 346	1010 ± 353	656 ± 366	1.0 (0.5-8.0)	2.3 ± 1.1
Reference	970 ± 344	1010 ± 346	651 ± 345	1.0 (0.3-5.0)	2.3 ± 1.0
***Ratio (90% CI)**	1.00 (0.95 – 1.06)	0.97 (0.89 – 1.05)	1.02 (0.90 – 1.15)	---	---
CV (%)	19.39	28.45	45.21	---	---

$AUC_{0-\infty}$ 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=70	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4643 ± 1897	4751 ± 1901	769 ± 390	2.3 (1.0-6.0)	6.2 ± 2.2
Reference	4732 ± 1804	4840 ± 1811	802 ± 415	2.3 (0.8-6.0)	6.2 ± 2.1
***Ratio (90% CI)**	0.97 (0.93 – 1.02)	1.01 (0.94 – 1.07)	0.96 (0.90 – 1.03)	---	---
CV (%)	15.61	23.24	23.46	---	---

$AUC_{0-\infty}$ 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=70	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1001 ± 296	1035 ± 300	141 ± 65	2.0 (1.0-3.5)	9.9 ± 2.2
Reference	1004 ± 276	1033 ± 280	142 ± 65	2.0 (1.0-3.0)	9.5 ± 1.8
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	1.00 (0.96 – 1.04)	1.00 (0.93 – 1.06)	---	---
CV (%)	15.35	14.87	23.29	---	---

$AUC_{0-\infty}$ 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*

Some small period effects were observed for the AUC_{0-t} and the C_{max} of losartan carboxy acid and the AUC_{0-t} of hydrochlorothiazide which are considered not to interfere with the bioequivalence testing. The residual coefficient of variation of the C_{max} of losartan is very high (45%) as can be expected of this compound. Additional confirmation of the validity of the results of losartan is that the residual coefficient of variation of the C_{max} of losartan carboxy acid is well below 30%. The pharmacological activity of this main metabolite of losartan is 10 – 40 time higher than the parent compound and also the variability in the pharmacokinetic parameters is smaller.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of losartan, under fasted conditions, it can be concluded that Kaliumlosartan + HCTZ axcount 100 mg/25 mg film-coated tablets and Fortzaar 100 mg/25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The data for metabolites losartan carboxy acid and hydrochlorothiazide are considered supportive.

The tested losartan-hydrochlorothiazide 100 mg/25 mg tablets are completely dose proportional with the losartan-hydrochlorothiazide 50 mg/12.5 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 100 mg/25 mg tablet may be extrapolated to the losartan-hydrochlorothiazide 50 mg/12.5 mg tablet.

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
During the mutual recognition procedure, the SPC and package leaflet were brought in line with the harmonised product information of losartan potassium hydrochlorothiazide containing products (art. 30 referral).

Readability test
For the readability test the MAH refers to the User Testing on readability performed for the comparable products Kaliumlosartan + HCTZ / Fairmed 50/12.5 and 100/25 mg. A separate readability test for the kaliumlosartan + HCTZ products at issue has not been performed, but bridging was proposed. In the submitted report the leaflet of both products have been compared to indentify potential differences which might influence the readability. The report concludes that there are no differences and a separate readability test is not necessary. The member states agreed with the approach and are also of the opinion that a new readability test is not necessary.
The lay-out and the design of the leaflet have been successfully tested for the comparable leaflet of Kaliumlosartan + HCTZ / Fairmed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kaliumlosartan + HCTZ axcount 50 mg/12.5 mg and 100 mg/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.

During the mutual recognition procedure, the SPC and package leaflet were brought in line with the harmonised product information of losartan potassium hydrochlorothiazide containing products (art. 30 referral). The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Kaliumlosartan + HCTZ axcount 50 mg/12.5 mg and 100 mg/25 mg tablets were authorised in the Netherlands on 16 April 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kaliumlosartan + HCTZ axcount tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 30 September 2008.

A European harmonised birth date has been allocated (15 February 1995) and subsequently the first data lock point for losartan-hydrochlorothiazide is February 2010. The first PSUR will cover the period from September 2008 to February 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 September 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