

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Losartankalium/Hydrochloorthiazide Ipcas 50/12.5 mg
film-coated tablets
Ipcas Produtos Farmaceuticos Unipessoal Lda, Portugal**

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/2618/001/DC
Registration number in the Netherlands: RVG 111595**

24 June 2013

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 for authorisation in NL:	27 May 2013
Concerned Member States:	Decentralised procedure with DE, DK, EE, ES, FR, IT, LT, LV, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Losartankalium/Hydrochlorothiazide Ipca 50/12.5 mg film-coated tablets from Ipca Produtos Farmaceuticos Unipessoal Lda. The date of authorisation was on 27 May 2013 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. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

The components of the Kaliumlosartan + HCTZ Arrow 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Hyzaar 50 mg/12.5 mg film-coated tablets (NL/H/1458/MR), which has been registered in the Netherlands by Merck Sharp & Dohme since 5 August 1996. In addition, reference is made to Hyzaar authorisations in the individual member states (reference product). The product is also marketed under the brand name Cozaar Comp.

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 Cozaar Comp 50/12.5 mg, 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 this product and no paediatric development programme has been submitted, as this is not required for a generic application.

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

Losartan potassium

The active substance losartan potassium is a well-known substance, which is described in the European Pharmacopoeia (Ph.Eur.*). The substance is a white or almost white, crystalline hygroscopic powder, which is freely soluble in water and methanol and very slightly soluble in acetonitrile. The drug substance exhibits polymorphism. Form I is manufactured consistently.

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

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with Ph.Eur. and the additional parameters as mentioned on the CEP. In addition the MAH has included limits for the particle size of the drug substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

Stability of drug substance

The retest period is 36 months when stored under the stated 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.

Hydrochlorothiazide

Hydrochlorothiazide is an established active substance described in the European Pharmacopoeia. The active substance is a white or almost white, crystalline powder, which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol (96 %). It dissolves in dilute solution of alkali hydroxides. The drug substance exhibits polymorphism. Form I is manufactured consistently.

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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with Ph.Eur. and the additional limits as mentioned on the CEP. In addition the MAH has included limits for the particle size of the drug substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six batches.

Stability of drug substance

The retest period is 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition

Losartankalium/Hydrochlorothiazide Ipc 50/12.5 mg is a yellow coloured, oval, biconvex, film-coated tablet.

The film-coated tablets are packed in PVDC/PVC-Aluminium blisters.

The excipients are: lactose monohydrate, microcrystalline cellulose, pregelatinized starch (maize), maize starch (dried), colloidal anhydrous silica, magnesium stearate, hypromellose 15cps, titanium dioxide (E171), talc (purified), macrogol 6000, quinoline yellow lake (E104) and purified water.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During development composition and process parameters were optimised until the final formulation was obtained. The composition of the batch used in the bioequivalence study is identical to the proposed final composition. Dissolution profiles of the drug product and the reference products have been included in the dossier. The results were comparable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process involves the following steps: sifting, dry mixing, granulation, wet milling and milling, drying, lubrication, compression, coating and packaging into the blisters. The manufacturing process is adequately validated on 3 pilot-scale and 3 full-scale batches. All parameters tested complied with the pre-set limits and no unexpected results were observed. The manufacturing process has been adequately described.

Control of excipients

The excipients used and their quantities, are common for immediate release tablets. Analytical procedures for all the excipients except the quinoline yellow lake are performed as per requirement specified in the Ph.Eur. A description of the analytical methods for quinoline yellow lake has been provided. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, average weight, loss on drying, uniformity of dosage units, related substances, dissolution, assay and microbial limits. The release and end-of-shelf-life specifications are identical for majority of the test procedures, exceptions concern the specifications for related substance and dissolution. The proposed limits for the various parameters are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from on three commercial-scale batches has been provided; all batches comply with the release specification.

Stability of drug product

Stability data on the product has been provided for three commercial-scale batches stored at 25°C/60%RH (36 months), 30°C/65% RH (36 months) and 40°C/75%RH (6 months). Furthermore, the following stability data for three additional commercial-scale batches of are available; 6 months data at accelerated conditions (40°C/75% RH), 9 months data at intermediate (30°C/65% RH) and long term (25°C/60% RH) conditions. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging material.

Based on results obtained at 40°C/75%RH it can be concluded that the drug product should be stored below 25°C. A photostability study was determined for the tablets in the original container as well as on the unpacked tablets. From the results it was observed that the product is stable when exposed in the packaging material, however not when directly exposed. In view of the stability results, a shelf-life of 36 months was granted, when stored below 25°C in the original blister in order to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only material of animal origin used. TSE statements of the various suppliers of the drug substances and excipients have been provided. TSE risk for the lactose used can be considered negligible.

II.2 Non-clinical aspects

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

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. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Losartankalium/Hydrochloorthiazide Ipca 50/12.5 mg (Ipca Produtos Farmaceuticos Unipessoal Lda, Portugal) is compared with the pharmacokinetic profile of the reference product Cozaar® Comp 50/12.5 mg 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 reference products in different member states.

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

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-38 years. Each subject received a single dose (one tablet: 50 mg losartan potassium + 25 mg hydrochlorothiazide) of one of the 2 formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

This is an acceptable design for a comparative bioavailability study. The wash-out period between the two treatments is long enough and the sampling schedule and period is sufficient. Plasma samples were analysed not only for the parent compound, but for the metabolite losartan acid as well. However, these data are not included in this report, as assessment is primarily based on the parent compound.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Four subjects dropped-out of the study due to the following reasons: fever (urinary tract infection), protocol violation (positive drug test for morphine in urine), personal reason (withdrew himself) and positive *widal* test (enteric fever). Forty-four subjects were included in the analysis.

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

Treatment N=44	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	464 ± 173	473 ± 176	213 ± 99	(0.5-3.5)	--
Reference	452 ± 173	462 ± 175	209 ± 98	(0.5-4.5)	--
*Ratio (90% CI)	1.03 (0.99-1.06)	1.03 (0.90-1.16)	1.02 (0.90-1.16)	--	--
AUC_{0-∞} 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					

**In-transformed values*

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

Treatment N=44	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	493 \pm 106	501 \pm 109	68 \pm 13	(1.0-4.5)	--
Reference	479 \pm 123	487 \pm 123	66 \pm 15	(1.25-4.5)	--
*Ratio (90% CI)	1.04 (1.00-1.08)	1.04 (0.99-1.11)	1.05 (0.99-1.11)	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.800-1.25. Based on the pharmacokinetic parameters of losartan and hydrochlorothiazide under fasted conditions, it can be concluded that Losartankalium/Hydrochlorothiazide IpcA 50/12.5 and Cozaar® Comp 50/12.5 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.

A total of 3 adverse events were reported in the test treatment group; vasovagal episode, fever and conjunctivitis. There were 2 adverse events reported in the reference treatment group; giddiness and urinary tract infection.

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 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

The combination of losartan and hydrochlorothiazide was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of the active substances can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The SPC is in line with the SPC of the reference product Cozaar Comp (NL/H/1458) and the latest version of the QRD template.

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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use.

There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 18 questions related to the content of the PL. Three questions were related to the structure/appearance of the PL. A satisfactory outcome was achieved when for each question, 90% of all participants are able to find the information requested within the PIL and 90% can show that they understand and can act upon it.

In round 1, the participants were able to answer over 90% of all questions and demonstrate that they could act accordingly in various situations. Based on quantitative and qualitative results from the first round, no changes were made to the PL for the second round of testing. In round 2, all participants were able to answer the questions.

In general, participants found the leaflet to be informative and well laid-out. Some participants thought the leaflet was too long; however, because the leaflet must be an accurate representation of the SPC, and properly convey all safety issues and warnings, the length of the leaflet cannot be shortened without jeopardizing its content and validity. One participant found the leaflet to be 'too technical'. Additionally, two participants commented on the font size being small. As a result, the mock-up was checked and it was confirmed that the text is presented using Times New Roman 9 point, which is agreed. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Losartankalium/Hydrochloorthiazide Ipca 50/12.5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Hyzaar 50 mg/12.5 mg film-coated tablets. Hyzaar 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 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Losartankalium/Hydrochloorthiazide Ipca 50/12.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 27 March 2013. Losartankalium/Hydrochloorthiazide Ipca 50/12.5 mg film-coated tablets was authorised in the Netherlands on 27 May 2013.

The date for the first renewal will be: 27 March 2018.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to include one batch annually into the stability program.

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
HCTZ	Hydrochlorothiazide
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 _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

