CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Entrizen/HCT 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg film-coated tablets
Merck Sharp & Dohme, the Netherlands

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/1606/001-003/DC
Registration number in the Netherlands: RVG 10318-20

14 October 2010

Pharmacotherapeutic group:	angiotensin II antagonists, plain
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 authorisation in NL:	28 July 2009
Concerned Member States:	Decentralised procedure with LV, AT (withdrawn on 18-9-09 [001&003] and on 21-1-09 [002]), BE (002 withdrawn on 19-12-08), CZ, DE, EE (withdrawn on 19-12-08), EL (withdrawn on 19-12-08), ES, FR, IT (002 withdrawn on 31-3-09), LU (not for 002), PT, SK, and ES (only 001 and 003)
Application type/legal basis:	Directive 2001/83/EC, Article 10c informed consent application

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 Entrizen/HCT 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg film-coated tablets, from Merck, Sharp & Dohme. The date of authorisation was on 28 July 2009 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 as 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.

Combination
The components of the Kaliumlosartan + HCTZ 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.

Regulatory history
For the Products Hyzaar 50/12.5 mg, Cozaar Plus 100/12.5 mg, and Fortzaar 100/25 mg an Art. 30 referral concerning the harmonisation of the product information was finalised in April 2008. As result of the referral all existing national marketing authorisation became MRP registrations, as if there has been a MRP. The Netherlands became the RMS for these products. Thereafter a type II variation to update module 3 (NL/H/1458/001-003/II/001) was finalised in October 2008.

In accordance with Article 10c of Directive 2001/83/EC, the current application consists of Module 1 with consent to Modules 2, 3, 4 and 5 for Hyzaar 50/12.5 mg, Cozaar Plus 100/12.5 mg, and Fortzaar 100/25 mg (NL/H/1458/001-003). The MAH for the informed consent application is the same as the one for the currently authorised products.

The quality overview presented in this PAR is based on the assessment reports for the type II variation to update module three (NL/H/1458/001-003/II/001).

All relevant pre-clinical and clinical data have been discussed during the article 30 referral concerning the harmonisation of the product information. Please see for discussion page http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Cozaar_Comp_30/WC500008584.pdf.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

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 – losartan postassium
Losartan potassium is an established active substances which is described in the United States Pharmacopoeia (USP*), and recently also in the European Pharmacopoeia (Ph.Eur.*). Losartan potassium is freely soluble in water. It shows polymorphism. Form I is the thermodynamically stable polymorph form at room temperature. It has no chiral centers. Full information on the manufacturing process of MSD has been provided.

Manufacture
The synthesis of losartan potassium consists of three steps. The used solvents and catalysts have been provided. Losartan potassium has been adequately characterised. Acceptable specifications have been adopted for both starting materials, the solvents and reagents.

Quality control of drug substance
At the time of assessment, losartan potassium was not described yet in the European Pharmacopoeia. The drug substance specification is in line with the Monograph of the United States Pharmacopoeia with additional requirements for bulk density, particle size and color and clarity of solution. 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 three full-scale batches from all proposed manufacturing sites.

Stability of drug substance
Stability data on the losartan have been provided for three full-scale batches stored for 48 months at 25°C/60%RH and (two batches) stored for six months at 40°C and ambient humidity. The batches were adequately stored. The stability results show that all results meet specifications and no trends are observed. The proposed re-test period of 48 months with no specific storage condition is approved.

Active substance – hydrochlorothiazide
Hydrochlorothiazide is an established active substance which is described in the European Pharmacopoeia. Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Polymorphism is not known and isomerism is not described.

The CEP procedure is used by one of the suppliers of the 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 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. For the other supplier, full information on the manufacturing process has been provided.

Manufacturing process
For one site the manufacturing process is covered by the CEP.
At the other site, hydrochlorothiazide is manufactured in three reaction steps, with two intermediates. Water is used as solvent in the final step. No catalysts are used. Hydrochlorothiazide has been adequately characterised, and acceptable specifications have been adopted for the starting material, the solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Monograph Hydrochlorothiazide of the European Pharmacopoeia with additional requirements for heavy metals, selenium and one particular impurity for material from one site and particle size and any other impurity for material from the other site.
The specification is acceptable in view of the route of synthesis and the various European guidelines, and the Ph. Eur. and USP Monograph. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches from both suppliers.

Stability of drug substance
For hydrochlorothiazide from one site, stability data on the active substance have been provided for three full scale batches stored for 60 months (two batches) or 48 months (one batch) at 25C/60%RH and one batch stored for thirteen months at 40ºC and ambient humidity. The batches were adequately stored. The stability results show that all results meet specifications and no trends are observed. The proposed re-test period of 60 months when stored below 25ºC is approved.
For the other site, the approved re-test of 5 years if when adequately stored as indicated on the Certificate of Suitability is approved.

** 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
Entrizen/HCT 50 mg/12.5 mg are yellow, oval film-coated tablets marked '*717*' on one side and plain or scored on the other. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Entrizen/HCT 100 mg/12.5 mg are white, oval film-coated tablets marked '*745*' on one side and plain on the other.
Entrizen/HCT 100 mg/25 mg are light yellow, oval film-coated tablets marked '*747*' on one side and plain on the other.

The film-coated tablets are packed in PVC/PE/PVDC blister packages with aluminum foil lidding, or HDPE bottles.

The excipients are - microcrystalline cellulose(E460), lactose monohydrate, pregelatinized maize starch, magnesium stearate (E572), hydroxypropyl cellulose (E463), hypromellose(E464).
Entrizen/HCT 50 mg/12.5 mg only - 4.24 mg (0.108 mEq) potassium, titanium dioxide (E171), quinoline yellow aluminum lake (E104), and carnauba wax (E903).
Entrizen/HCT 100 mg/12.5 mg only - 8.48 mg (0.216 mEq) potassium, white color concentrate [which contains titanium dioxide (E171)] and carnauba wax (E903).
Entrizen/HCT 100 mg/25 mg only - 8.48 mg (0.216 mEq) potassium, titanium dioxide (E171), quinoline yellow aluminum lake (E104), and carnauba wax (E903).

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The outline of the development was to develop a combination product with similar characteristics as the marketed, individual component tablet formulations. The choice of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been described sufficiently for each strength.

Entrizen/HCT 50 mg/12.5 mg - results of batch analysis have been provided for three commercial-scale batches manufactured one site.

Entrizen/HCT 100 mg/12.5 mg - the manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches manufactured at two sites.

Entrizen/HCT 100 mg/25 mg - process validation data on the product has been presented for three batches manufactured at one site.

Quality control of drug product

The product specification includes tests for identity, assay, dissolution, degradation products and content uniformity for both active substances, identity titanium dioxide and quinoline yellow (not for 100 mg/12.5 mg strength), appearance of tablet and microbial limits. The release and shelf-life requirements are acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from two sites have been provided on one production-scale and two pilot-scale batches, demonstrating compliance with the release specification.

Stability tests on the finished product

50 mg/12.5 mg - Stability data on the product has been provided for three batches, 36 months stored at 25C/60% RH and three batches stored for 6 months at 40°C/75%RH, manufactured at one site. The batches were adequately stored. At 25°C/65%RH 36 months all results comply. At 40°C/75%RH an increase of one specific impurity is observed resulting in out of specification results.

100 mg/12.5 mg - Stability data on the product has been provided for two pilot-scale batches, 36 months stored at 25C/60% RH and 30C / 65% RH and 6 months at 40C/75% RH, manufactured at the development site and for thee full-scale batches, 24 months at 30C/65% RH, manufactured at the proposed site. The conditions used in the stability studies are according to the ICH stability guideline. The batches were adequately stored. The only trend observed is degradation of hydrochlorothiazide at 40°C/75%RH with results out of specification. At the other conditions all results complied and therefore the proposed shelf-life of 36 months, stored not above 30°C, is approved. Additional stability results of the full-scale batches covering the whole shelf-life are awaited to fully support the approved shelf-life.

100 mg/25 mg - Stability data on the product has been provided for three batches, 36 months stored at 25°C/60% RH and 6 months stored at 40°C/75%RH, manufactured one site. The batches were adequately stored. No trends are observed and all results comply. The data justify the proposed shelf-life of 36 months, stored in the original packaging, not above 30°C.

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

Pre-clinical data have been discussed during the referral procedure. See page http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Cozaar_Comp_30/WC500008584.pdf. for discussion.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of losartan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Clinical data have been discussed during the referral procedure. See page http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Cozaar_Comp_30/WC500008584.pdf. for discussion.

Risk management plan
Losartan was first approved in 15 February 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of losartan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or 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 consistent with that of other losartan+HCTZ containing products. The SPC, package leaflet and labelling are in the agreed templates. Section 4 and 5 are in line with the SPC concluded by the CHMP in their plenary meeting from 21 to 24 April 2008, by consensus under Article 30 of Directive 2001/83/EC.

Readability test
A readability test has been performed during the referral procedure.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Entrizen/HCT 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg film-coated tablets have a proven chemical-pharmaceutical quality, and have a favourable efficacy and safety profile.

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 other losartan+HCTZ containing products. The SPC, package leaflet and labelling are in the agreed templates. Section 4 and 5 are in line with the SPC concluded by the CHMP in their plenary meeting from 21 to 24 April 2008, by consensus under Article 30 of Directive 2001/83/EC.

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 decentralised procedure was finished on 21 April 2009. The other member states mutually recognised the Dutch evaluation for the marketing authorisation.

A European harmonised birth date has been allocated (15 February 1995) and subsequently the first data lock point for losartan is February 2010. The first PSUR will cover the period from July 2009 to October 2010 after which the PSUR submission cycle will be 3 years.

The first renewal application was made on 11 December 2009 to the RMS and all CMS. See Annex I.

There were no specific 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
Change in the name of the medicinal product.	NL/H/1606/ 001-003/IB/ 001	IB	13-8-2009	12-9-2009	Approval	N
Change in pack size of the finished product. Change in the number of units in a pack. Change within the range of the currently approved pack sizes.	NL/H/1606/ 001/IA/002	IA	30-9-2009	14-10-2009	Approval	N
Change in coating weight of tablets or change in weight of capsule shells. Immediate release oral pharmaceutical forms.	NL/H/1606/ 001/IA/003	IA	7-10-2009	21-10-2009	Approval	N
Renewal of the marketing authorization.	NL/H/1606/ 001-003/R/ 001	Renewal	11-12-2009	3-5-2010	Approval	Y, Annex I
Change in the name and/or address of the marketing authorisation holder: move of MAH in Belgium and Luxembourg	NL/H/1606/ 001&003/IA /003/G	IA/G	19-7-2010	18-8-2010	Approval	N

Annex I - Renewal Marketing Authorization

I Recommendation

Based on the review of the data on quality, safety, and efficacy the Member states consider that the Renewal for NL/H/1606/001-003/R/001 Entrizen/HCT 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg film-coated tablets is approved for unlimited time.

This renewal ran in parallel with the renewal for Cozaar Comp (NL/H/1458/001-003/R/001).

II Scope

For this renewal, the MAH has submitted the following documents.

- Ten PSURs covering the period from 15 august 2004 to 14 August 2009.
- A Summary Bridging Report covering the period 15 August 2004 to 14 August 2009.
- A Clinical Expert Statement, dated 23 September 2009.
- The SPC in English.

III Actions taken for safety reasons

No specific actions for safety reasons have been taken to date, either by the regulatory authorities or by the marketing authorisation holders of the losartan potassium/hydrochlorothiazide within Merck Sharp & Dohme B.V.

IV Changes to the Reference safety information

The MAH used the Worldwide Product Circular (WPC), latest version dated 12 December 2008, as Reference Safety Information (RSI).
During the period under review changes were made to two (2) sections in the RSI:

- Side effects
- Drug interactions

This is acceptable, the SPC has been updated in accordance with these changes.

V Adverse reactions

During the reporting period, 3,503 spontaneous reports from healthcare providers and 47 study reports were received, including 833 reports with serious events.

The Adverse Reaction Reports (ADRs) occurred most frequently in the following Medra System Organ Classes (SOCs): Skin and subcutaneous tissue disorders (1197), Nervous system disorders (501), Metabolism and nutrition disorders (444), Investigations (420) and General disorders and administration site conditions (403).

The most frequently reported adverse events were photosensitivity reaction (637, listed), hyponatremia (191, listed), dizziness (161, listed), rash (142, unlisted in the RSI, but included in the SPC) and hypokalemia (104, listed). The most frequently reported unlisted serious adverse reactions were syncope (17, unlisted in the RSI, but labelled in the SPC), drug interaction (15), fall (14) and cerebral infarction (14).

The adverse reaction reports mentioned above are most likely due to underlying diseases, concomitantly administered medication, are considered to be isolated cases, or are sufficiently covered by current SPC. Therefore, no action is required.

VI Fatal cases

During the period under review 40 cases reporting a fatal outcome were received. Based on these cases, no action is required.

VII Studies

There were no newly analysed company-sponsored studies and no targeted new studies during the reporting period.

Published studies

During the reporting period there were four (4) published safety studies identified in the scientific literature:

Zang R, Witkowski S, Fu Q, Classen J A H R and Levine B D. Cerebral hemodynamics after short- and long-term reduction in blood pressure in mild and moderate hypertension. *Hypertension*. 2007; 49(5); 1149-1155.

Watanabe LA, Wei M, Sun N, et al. Effect on blood pressure control of switching from valsartan monotherapy to losartan/hydrochlorothiazide in Asian patients with hypertension: results of a multicentre open-label trial. *Curr Med Res Opin*. 2006; 22(10); 1955-1164.

Macias-Nunez JF, Bustamante J, Ghais Z, et al. Pharmacovigilance study of the safety and effectiveness of losartan therapy: Long-term effects of losartan alone or in combination on uricemia. Rev Esp Geriatr Gerontol. 2006; 41(1); 13-20.

Sarute T, Ogihara T, Matsuoka H, et al. Antihypertensive Efficacy and Safety of Fixed-Dose Combination Therapy with Losartan plus Hydrochlorothiazide in Japanese Patients with Essential Hypertension. *Hypertense Res* 2007; 30(8); 729-739.

Based on the presented articles no action is required.

VIII Conclusion on safety

No new safety issues were identified based on spontaneous reports, literature or published studies.

IX Overall conclusion and benefit-risk assessment

Based on the data accumulated during the review period, the benefit/risk ratio for the product remains favourable. There have been no new safety issues identified in the period under review. The renewal is granted with unlimited validity.
The MAH committed to file the appropriate variation to align the drug substance specification losartan potassion with the Ph. Eur. monograph within 6 months of approval of the renewal.
As losartan potassium/hydrochlorothiazide takes part in the PSUR synchronisation project of the Heads of Medicines Agencies. The next PSUR should cover the period from 15 February 2010 to 14 February 2013 and should be submitted within 60 days from the data lock point.