CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cozaar 12.5 mg, 50 mg, and 100 mg film-coated tablets Merck Sharp & Dohme B.V., the Netherlands

losartan (as potassium)

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/1457/001-003/E001
Registration number in the Netherlands: RVG 101836, 17617, 26791

2 July 2010

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA01
Route of administration:	oral
Therapeutic indication:	essential hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment; chronic heart failure (in patients ≥ 60 years) when treatment with ACE inhibitors is not considered suitable due to incompatibility or contraindication; reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.
Prescription status:	prescription only
Date of first authorisation in NL:	22 May 2008 (12.5 mg), 14 March 1995 (50 mg), 5 March 2002 (100 mg)
Concerned Member States:	Repeat-use procedure with: *12.5 mg* – BG, CY, CZ, FR, LV, MT, RO, SK, UK; *50 mg and 100 mg* – CZ and SK.
Application type/legal basis:	Directive 2001/83/EC, Article 8(3) full-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 Cozaar 12.5 mg, 50 mg, and 100 mg film-coated tablets, from Merck Sharpe & Dohme. The date of authorisation was on 22 May 2008 (12.5 mg), 14 March 1995 (50 mg), and 5 March 2002 (100 mg), respectively, in the Netherlands.

The product is indicated for treatment of:

- essential hypertension.
- renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
- reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.

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

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 aldosteron. 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.

Regulatory history
Initially, the three Cozaar strengths were registered separately in the Netherlands, each by a National procedure. However, an Art. 30 referral concerning the harmonisation of the product information, was initiated by the European Commission, during which pre-clinical and clinical data were discussed by The Committee for Medicinal Products for Human Use (CHMP). The CHMP finalised the referral in their plenary Meeting from 21 to 24 April 2008 by consensus under Article 30 of Directive 2001/83/EC, recommending the harmonisation of the product information across the European Union for Cozaar 12.5 mg, 25 mg, 50 mg and 100 mg film-coated tablets. As result all existing national marketing authorisation became MRP registrations, as if there had been an MRP. The Netherlands became the RMS for these products.

To obtain a marketing authorisation in countries where Cozaar was not registered yet, a repeat use MRP (NL/H/1457/001-003/E001) was started. The repeat-use procedure is described in this PAR. In parallel a type II variation to update module 3 (NL/H/1457/001-003/II/001 see Annex I) in all countries was submitted. The repeat-use procedure and the type II variation followed the same time table.

Line extension
On 23 October 2008, the CHMP gave a positive opinion for a line-extension under Article 29 of the Paediatric Regulation (EC) 1901/2006 for Cozaar and associated names (losartan potassium), from Merck Sharp & Dohme BV, to add a paediatric formulation of powder and solvent for oral suspension. This was the first recommendation for a line-extension relating to a new pharmaceutical form for use in the paediatric population on the basis of data generated in accordance with an agreed paediatric investigation plan (PIP). The paediatric formulation has been developed for the treatment of essential hypertension in children and adolescents 6-16 years of age.
At 22 January 2009, the Commission Decision for the new paediatric formulation for Cozaar which was evaluated under Article 29 of the Paediatric Regulation was available. Based on this Decision national marketing authorisations for the Cozaar powder and solvent for oral suspension, to comply with the EC decision, were granted in the EU countries.
The national line-extension MAs for the oral suspension are included in the MRP with NL as RMS (NL/H/1457/004).
For the line-extension a type II variation to update module 3 (NL/H/1457/004/II/004 see Annex II) in all countries was submitted.

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/pdfs/human/referral/cozaar/cozaar_annexI_III_en.pdf of the EMA website.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC, full-application with known active substance. Furthermore this is an application for a type II variation for all other countries which are not involved in the repeat use MRP in order to update module 3. The type II variation will have the same time table as the repeat use MRP.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is losartan potassium, an established active substance 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 has been provided.

Manufacture
The synthesis consists of three steps. The used solvents and catalysts have been provided. Losartan potassium has been adequately characterised with UV-, IR-, Proton Magnetic Resonance-, Carbon-13 Magnetic Resonance-, and Mass spectroscopy. 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 both proposed manufacture sites.

Stability of drug substance
Stability data on the active substance 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.

* *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
Cozaar 12.5 mg are blue, oval film-coated tablets marked *11* on one side and plain on the other.
Cozaar 50 mg are white, oval film-coated tablets marked *952* on one side and scored on the other.
The tablet can be divided into equal halves.
Cozaar 100 mg are white, teardrop-shaped film-coated tablets marked *960* on one side and plain on the other.
The film-coated tablets contain respectively 12.5, 50 or 100 mg losartan potassium.

The tablets are packaged in PVC/PE/PVDC blister packages with push-through aluminum foil lidding, or in HDPE bottles.

The excipients are: microcrystalline cellulose (E460), lactose monohydrate, pregelatinized maize starch, magnesium stearate (E572), hydroxypropyl cellulose (E463), hypromellose (E464) potassium, carnauba wax (E903), and titanium dioxide (E171).
Only 12.5 mg – indigo carmine (E132) aluminium lake.

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

The 50 mg and 100 mg tablets are dose proportional identical. The 12.5 mg tablet contains the same excipients as the 50 and 100 mg tablet, with additionally the colorant, yet is not dose proportional

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Discussed issues are: choice for direct compression, choice for filmcoating, size and weight tablets, choice excipients and their grades, formulation optimalisation, lubrication process vs content uniformity, compression force, effect particle size of active on flow ability, compression and dissolution. The choice of the packaging and manufacturing process are justified. Results of batch analysis of the batches used in the clinical studies have been provided.

Manufacturing process
The active substances are dry mixed with the microcrystalline cellulose, lactose monohydrate and corn starch. The blend is lubricated with magnesium stearate and compressed into tablets. The tablets are coated and waxed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches of all strengths.

Excipients
The colorant complies with EU Directive 95/45/EC. The excipients comply with European Pharmacopoeia requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for identity, assay, dissolution, degradation products and content uniformity, identity titanium dioxide and, for 12.5 mg tablet, indigo carmine, 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 the manufacture site have been provided of three batches of all strengths, demonstrating compliance with the release specification.

Stability of drug product
Shelf-life and storage conditions have been approved based on submitted stability results of storage at normal and accelerated storage conditions, in line with the ICH Guidelines. The shelf-life of the tablets is 36 months, stored in the original package to protect from moisture and light. An additional storage requirement, '*Do not store above 25°C*', is applicable for the tablets stored in the HDPE tablet container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only substance of ruminant animal origin present in the product or used in the manufacturing of this product. It is declared that the lactose is derived from milk certified to originate from healthy animals and is collected in the same manner as milk fit for human consumption and that the lactose is not prepared with the use of other ruminant materials with the possible exception of calf rennet. Under these conditions, a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

Pre-clinical data have been discussed during the referral procedure. See page http://www.ema.europa.eu/pdfs/human/referral/cozaar/cozaar_annexI_III_en.pdf of the EMEA website 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/pdfs/human/referral/cozaar/cozaar_annexI_III_en.pdf of the EMEA website for discussion.

Risk management plan
Losartan was first approved in 1994, 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 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

SPC
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.
After approval, SPC sections 4.1, 4.2 and 5.1 were changed by type II variation NL/H/1457/001-003/II/002. One pivotal study was submitted to support the proposed changes regarding the information

for treatment of proteinuria to a pediatric patient population with renal disease. See annex I (page 9) for an elaborate discussion of this variation.
In addition, another type II variation NL/H/1457/004/II/004 was submitted to change SPC sections 4.2 and 5.1. to extend the information for treatment of proteinuria to a paediatric patient population with renal disease for *Cozaar 2,5 mg/ml powder and solvent for oral suspension*. See annex II (page 25) for an elaborate discussion of this variation. Note that changes proposed in SPC and supporting data submitted are identical to the approved type II variation 1457/II/002 for the Cozaar tablets

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

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cozaar 12.5 mg, 50 mg, and 100 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 containing producst. 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. Cozaar was authorised in the Netherlands on 22 May 2008 (12.5 mg), 14 March 1995 (50 mg), and 5 March 2002 (100 mg).

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The repeat-use procedure was finished on 1 October 2008. The type II variation regarding this procedure (variation NL/H/1457/001-003/II/001) was also finished on this date and was positively concluded. The other member states mutually recognised the Dutch evaluation for the marketing authorisation.

A European harmonised birth date has been allocated (2 September 1994) and subsequently the first data lock point for losartan is September 2010. The first PSUR will cover the period from 1 October 2008 to September 2010, after which the PSUR submission cycle is 3 years.

The renewal date was 31 December 2009, and therefore the first renewal application was made on 29 May 2009 to the RMS and all CMS. See Annex III.

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
Update Module 3	NL/H/1457/ 001-003/II/001	II	3-7-2008	1-10-2008	Approval	N
Update product information for the Cozaar tables with paediatric data from study protocol 326	NL/H/1457/ 001-003/II/002	II	17-12-2008	6-4-2009	Approval	Y, Annex I
SPC update following PSUR release, implementation PhVWP for pregnancy and lactation and revisions from Art 29 as applicable to the tablets	NL/H/1457/ 001-003/II/003	II	16-1-2009	29-6-2009	Approval	N
Update product information of the Cozaar suspension with paediatric data from study protocol 326. Changes proposed in SPC and supporting data submitted are identical to the approved type II variation 1457/II/002 for the Cozaar tablets.	NL/H/1457/ 004/II/004	II	15-5-2009	16-7-2009	Approval	Y, Annex II
Addition of alternate bottle with different dimensions for the packaging of Ora-Blend SF.	NL/H/1457/ 004/IA/005	IA	13-5-2009	27-5-2009	Approval	N
Addition of an alternate closure with a different qualitative/quantitative composition for the packaging of Ora-Blend SF.	NL/H/1457/ 004/IB/006	IB	13-5-2009	12-6-2009	Approval	N
Clarification of the description of the liner used in the packaging of Ora-Blend SF.	NL/H/1457/ 004/IB/007	IB	13-5-2009	11-6-2009	Approval	N
Renewal of the Marketing Authorization.	NL/H/1457/ 001-003/R/ 001	Renewal	29-5-2009	9-11-2009	Approval	Y, Annex III

ANNEX I – Type II variation NL/H/1457/001-003/II/002

I Recommendation

Based on the review of the data on safety and efficacy, the RMS considers that the variation application for Cozaar® 12.5, 50 and 100 mg to section 4.1, 4.2 and 5.1 of the SPC to extend the SPC with information on paediatrics, is approvable.

Major objections have been solved and the SPC has been amended accordingly.

In addition, the amendment in section 4.1 according to the Article 29 referral, procedure number EMEA/H/A-29-PAD/1022 (decision dated 22 January 2009), is acceptable.

II Executive Summary

II.1 Scope of the variation

MSD submitted a type II variation for Cozaar® tablets for paediatric patients via the Mutual Recognition Procedure. The application concerns changes proposed to the SPC in section 4.1, 4.2 and 5.1, to extend the information for treatment of proteinuria to a pediatric patient population with renal disease. To support these changes one pivotal study was submitted. The pivotal study included children aged 1 to 17 years with proteinuria from a wide range of etiologies. The objectives and design of the study were discussed in CHMP scientific advice and agreed upon with the Paediatric Committee (PDCO) in the Paediatric Investigational Plan. In addition to this study, the MAH is further studying paediatric hypertension development in lower age groups through a dose ranging trial in hypertensive children 6 months to 6 years old.

In the first round major objections were raised with regard to the control group in hypertensive patients, with respect to level of blood pressure control and conflicting results in normotensive patients in the SPC.

The SPC is harmonized in accordance with an Article 29 referral (EMEA/H/A/A-29-PAD/102) to ensure consistency of the SPC information.

The MAH has submitted the dossier to the MEB and the CMSs involved in the MRP. Cozaar is approved for the indications:

- *Treatment of essential hypertension.*
- *Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.*
- *Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.*
- *Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).*

In the Netherlands, Cozaar was first authorized in 1995. After an Article 30 referral in September 2008 the nationally authorised summaries of product characteristics, package leaflet and labelling were harmonised via a MRP procedure with the Netherlands as Reference Member State.
At the time of this type II variation, no RAAS agents were approved in the EU for the treatment of paediatric proteinuria. Following the Article 29 referral, procedure number EMEA/H/A-29-PAD/1022 (decision dated 22 January 2009), losartan has also been approved for the treatment of hypertension in children aged 6 to 16 years old.

II.2 Supplementary paragraph

Losartan is an oral, specific, and selective angiotensin-II receptor (type AT1) antagonist. *In vitro* and *in vivo*, both 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 synthesis.
RAAS inhibitors are advocated as first choice antihypertensive drugs in patients with proteinuria and hypertension. In general in an adult population, a single antihypertensive drug is not sufficient to achieve optimum blood pressure control. The RENAAL and IDNT studies demonstrated that 3-4 antihypertensive drugs are needed in hypertensive patients with severe diabetic proteinuria to achieve blood pressure targets. Losartan (and irbesartan) demonstrated to give additional decline in proteinuria beyond blood pressure control – in those with optimised antihypertensive therapy -, eventually resulting in a significant decline in the risk of need for renal transplantation or long-term dialysis. The benefit of treating normotensive adults with proteinuria has however not been unequivocally demonstrated and an indication as such is currently not granted.

III Scientific discussion

III.1 Quality aspects

No new data have been submitted.

III.2 Non clinical aspects

No new data have been submitted.

III.3 Clinical aspects

The purpose of the study was to evaluate the effects of losartan treatment on proteinuria reduction in children and adolescents up to 17 years old. The submitted pivotal study to support such changes was a multicenter, randomized, double-blind, parallel, placebo or amlodipine-controlled study of the effects of losartan on proteinuria in pediatric patients with or without hypertension.

III.3.1 Clinical pharmacology

No new data have been submitted.

III.3.2 Clinical efficacy

Main study

MK-0954 (Protocol 326): A Randomized, Double-Blind, Parallel, Placebo or Amlodipine-Controlled Study of the Effects of Losartan on Proteinuria in Paediatric Patients With or Without Hypertension.

Aim of the study
To study the effects of losartan compared to placebo (non-hypertensives) or amlodipine (hypertensives) on reduction of proteinuria in children and adolescents up to 17 years of age with hypertension (if ≥6 years old) and without hypertension (if ≥1 year old). To determine whether losartan is well tolerated at a dose of up to 1.4 mg/kg/day (up to a maximum daily dose of 100 mg) in paediatric patients with proteinuria.

Comments RMS
The use of losartan in children and adolescents with proteinuria and who are hypertensive can be considered in line with the currently approved renoprotective indication in hypertensive Type 2 diabetes mellitus (T2DM) patients. The use of losartan in children and adolescents with proteinuria and who are normotensive is a new approach with a different etiological disease background. The provided study only demonstrates short term decline in proteinuria. It is agreed that treating proteinuria in hypertensive and non-hypertensive patients is more and more accepted as clinical practice. However, treatment with losartan is only indicated for lowering proteinuria in adults as part of other antihypertensive treatment. It is difficult to predict whether a short-term proteinuria decline will lower proteinuria in the long term or what

the impact will be on renal function per se. Therefore, the long-term 3-year data of the extension study are eagerly awaited to provide a better understanding of the long-term renal effects.

The used dose was justified based on previous work in hypertensive patients (Shahinfar, AJH 2005, 183-190 and Ellis, Am J Hyp 2004, 928-935). Although this is not a good justification for the treatment of normotensive patients, the dose in this patient group is based primarily on the highest tolerable dose and the hypotensive response. Blood pressure monitoring is essential, particularly in these patients. This is sufficiently reflected in the SPC.

In conclusion, proteinuric effects of losartan in hypertensive children are considered in line with the adult indication, despite the different etiology (no diabetes) and although long-term efficacy has not been shown. The discordance between treatment of normotensive paediatric patients in relation to the current adult indication remains. However, the MAH has described these shortcomings acceptably in the SPC (sections 4.2 and 5.1).

Patients
306 patients (aged 6-17 if hypertensive; aged 1-17 if normotensive) with history of proteinuria associated with chronic renal disease of any etiology, stable urine protein/creatinine ratio of ≥0.3 g/g based upon the mean of three samples obtained at baseline, and glomerular filtration rate of ≥30 ml/min/1.73m2, as determined by the Schwartz formula.

Comments RMS
These patients are considered to have severe proteinuria, however with important differences in underlying etiologies compared to adults. A distinction should be made between the patients who are normotensive and the patients who are hypertensive. The latter patients could be considered more comparable to the RENAAL adult population.

Design
The study was a randomized, double-blind, parallel and/or placebo controlled study. The study consisted of a 4-week single-blind run-in period intended to wash patients off RAAS and other anti-hypertensive agents, followed by a 12-week double-blind base period. During the single-blind run-in period, patients received amlodipine suspension (hypertensive stratum) or losartan placebo suspension (normotensive stratum).

A 3 years open-label extension comparing losartan with enalapril is ongoing. Proteinuria assessment and other safety laboratory tests (hematology, cystatin C, serum chemistry and urine protein/creatinine ratio) will be obtained. In addition, blood pressure, along with other vital signs, will be measured at each visit. The extension will provide information on the long-term effects of losartan.

Comments RMS
The study design shows similarities to the IDNT study, where irbesartan was compared to placebo and amlodipine in hypertensive T2DM patients with proteinuria. The amlodipine arm was added to assess blood pressure independent effects in reduction of proteinuria. Therefore, the design is considered appropriate for the hypertensive group.
However, the design is complicated with respect to the evaluation of an effect in normotensive patients. As no other antihypertensive drug is introduced in the control placebo arm, a difference in blood pressure control can be expected between the active and control arm that may affect both efficacy and safety outcomes.

The MEB does not agree with the MAH's opinion that the etiology of renal disease in normotensive and hypertensive paediatric patients is similar. However, in general, it can be assumed that hypertension has played / plays an important role in the (further) development of renal disease in the hypertensive subgroup. Although the etiology in this hypertensive subgroup differs from that of an adult population, it seems reasonable to expect renal protective effects in children as well, based on observed decline in proteinuria as has been acknowledged in the adult indication for renoprotection in hypertensive T2DM patients.

Therefore, it is agreed that this information is included in section 5.1. However, long-term efficacy has still to be established. A caveat is the discordance of including information on the treatment of normotensive paediatrics versus the current indication of losartan only for adults with proteinuria as part of hypertenisve treatment. However, this has been acceptably reflected in the SPC. Although similar subtypes are mentioned, the distribution across these subtypes is different.

Measuring efficacy
The applicant assessed 3 urine samples at day 0 and after 12 weeks for assessing the protein/creatinine ratio. One urine sample was taken at 4 and 8 weeks.

Safety was assessed by physical examinations, vital signs measurements, laboratory safety evaluations and by adverse experience monitoring.

Comments RMS
The way efficacy is measured is considered appropriate.

Efficacy assessment

Primary endpoint:
The primary endpoint was the change in proteinuria (logarithmic transformation urinary protein excretion (g protein/g creatinine)) after 12 weeks on losartan compared to control (amlodipine in the hypertensive group, placebo in the non-hypertensive group).

Secondary endpoints:
Frequency of clinical and laboratory adverse events, physical examination including height measurement and Tanner Staging, vital signs (pulse rate, blood pressure and weight), and laboratory safety evaluations (serum chemistry, hematology, fasting lipids, cystatin C, calculation of GFR, and urine pregnancy testing if applicable).

Comments RMS
The primary and secondary endpoints are considered appropriate. Important secondary endpoints as blood pressure and GFR are also included.

Results

Patient demographics at baseline

Patients in the losartan group were 10.4 years of age (1 to 17) and in the amlodipine/placebo group 9.7 (1 to 17).
The patient demographics particularly related to the primary outcome are presented below. The Pr/Cr ratio is slightly higher for the control group as is the diastolic and systolic blood pressure

Table 1: Patient demographics of laboratory values related to the primary outcome

	Losartan (N=152)	Amlodipine/Placebo (N=154)	Total (N=306)
Pr/Cr Ratio (gm/gm)			
N	151	154	305
Mean	2.2	2.8	2.5
SD	2.6	3.8	3.3
Median	1.0	1.4	1.3
Range	0.1 to 11.8	0.1 to 26.6	0.1 to 26.6
GFR (ml/min/1.73m^2)†			
N	151	154	305
Mean	119.6	117.9	118.7
SD	49.2	53.2	51.2
Median	117.9	123.5	120.1
Range	16.3 to 295.6	29.4 to 289.4	16.3 to 295.6
Cystatin-C (mg/L)			
N	143	145	288
Mean	11.5	12.7	12.1
SD	5.9	7.1	6.5
Median	9.0	10.0	10.0
Range	6.0 to 45.0	5.0 to 43.0	5.0 to 45.0
SiSBP (mmHg)			
N	152	154	306
Mean	106.0	107.2	106.6
SD	13.4	13.8	13.6
Median	106.0	106.5	106.0
Range	72.0 to 137.0	76.0 to 142.0	72.0 to 142.0
SiDBP (mmHg)			
N	152	154	306
Mean	66.8	67.8	67.3
SD	10.7	11.6	11.2
Median	66.5	67.0	67.0
Range	42.0 to 91.0	46.0 to 100.0	42.0 to 100.0

10 patients (2 on losartan and 8 on placebo) were randomized with a Pr/Cr ratio at randomization less than 0.3.

Comments RMS
With these numbers of patients it is difficult to reach a full comparable randomization. Slight differences therefore appear. These are however not considered to extensively influence outcome.

Patient disposition

More patients discontinued in the control group than in the active group mostly related to adverse events.

Table 2: Patient disposition

	Losartan (N=152)		Amlodipine/Placebo (N=154)		Total (N=306)	
	n	(%)	n	(%)	n	(%)
Treated	152	(100.0)	154	(100.0)	306	(100.0)
Discontinued†	7	(4.6)	11	(7.1)	18	(5.9)
Adverse event	1	(14.3)	4	(36.4)	5	(27.8)
Deviation from protocol	3	(42.9)	2	(18.2)	5	(27.8)
Lost to follow-up	1	(14.3)	1	(9.1)	2	(11.1)
Physician decision	1	(14.3)	2	(18.2)	3	(16.7)
Progressive disease	0	(0.0)	1	(9.1)	1	(5.6)
Withdrew consent	1	(14.3)	1	(9.1)	2	(11.1)
Completed	145	(95.4)	143	(92.9)	288	(94.1)

† Percentage at sub-category levels are calculated using the total number in the category as the denominator.

Comments RMS
A larger number in the amlodipine/placebo group discontinued due to adverse events. The numbers are small and are not expected to affect outcome in a significant manner.

Statistical analysis
The primary endpoint was analyzed using a mixed model for the change from baseline in urinary protein excretion (on a the logarithmic scale) with fixed effect terms for treatment (losartan versus placebo/amlodipine), stratification factor 1 (hypertensive or not), and stratification factor 2 (prior ACE-I/ARB use or not), time, treatment by time interaction and baseline urinary protein excretion (on the logarithmic scale), a random effect for patient and an unstructured variance-covariance was used.

Adjusting for time-varying covariates, a mixed model for the change from baseline in urinary protein excretion (on the logarithmic scale) with fixed effect terms for treatment (losartan versus placebo/amlodipine), stratification factor 1 (hypertensive or not), and stratification factor 2 (prior ACE-I/ARB use or not), time, DBP, SBP, treatment by time interaction and baseline urinary protein excretion (on the logarithmic scale), a random effect for patient and an unstructured variance-covariance. The treatment effect when adjusted for a timevarying covariate should however be interpreted cautiously because the time-varying covariate may be related to the treatment effect during the trial.

Comments RMS
The choice of the statistical tests is considered appropriate. The expected difference and number of patients included is justified.

Efficacy results

Primary endpoint
Reduction in proteinuria after 12 weeks of treatment was 35.8% (95% CI 27.55,43.11) on losartan (n=150) versus a 1.38% (95% CI -14.51,10.27) increase on amlodipine or placebo (n=152), and this difference was highly statistically significant, $p < 0.001$. In absolute figures, losartan reduced proteinuria from 1.27 (SD 2.30) g/g to 0.83 (SD 2.48). For amlodipine/placebo this was 1.55 (4.81) to 1.60 (6.73).

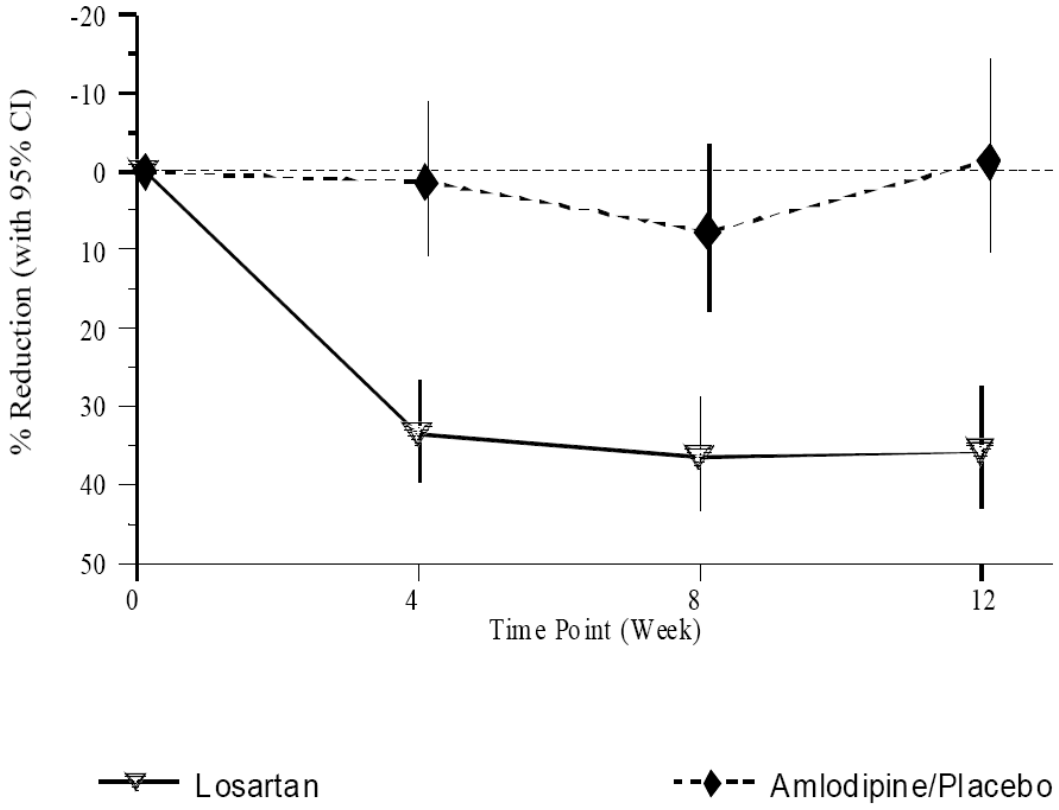

Figure 1: Percentage reduction in proteinuria (Pr/Cr ratio) after 12 weeks of treatment.

Secondary endpoint

Treatment with losartan resulted in a greater mean blood pressure decline than with amlodipine: SBP/DBP of -5.5/-3.8 mm Hg on losartan vs. -0.1/+0.8 mm Hg on amlodipine. Treatment with losartan resulted in a greater mean blood pressure decline than with placebo: SBP/DBP of -3.7/-3.4 mm Hg on losartan vs. 0.1/+0.6 mm Hg on placebo.

According to the applicant, difference in proteinuria change from baseline between losartan and amlodipine/placebo remained highly significant after adjustment for change in blood pressure (systolic and diastolic blood pressure): decreases of 36.64% versus 3.90%, respectively, $p < 0.001$

Although the study was not powered to demonstrate significant differences in proteinuria change from baseline within the 2 strata, the difference between losartan and amlodipine in the hypertensive stratum was 41.47% (95%CI 29.94;51.11) decrease vs. 2.43% increase (95%CI -22.16;14.11), respectively; and between losartan and placebo in the normotensive stratum, 34.36% (95%CI 25.19;42.41) decrease vs. 2.63% increase (95%CI -17.03;10.01) , respectively.

Subgroup analysis

Reduction in proteinuria was consistently observed across all pre-specified subgroups, including etiology of proteinuria (glomerular versus non-glomerular, uropathic/dysplastic versus non-uropathic/dysplastic), as well as age, gender, race, Tanner stage, weight, prior RAAS agent use, and geography.

Figure 2 shows that the magnitude of proteinuria reduction was remarkably consistent across subgroups, including by age (above and below the median age of 11 for the total study population). This consistency was also observed across the normotensive and hypertensive strata (Tables 3 and 4).

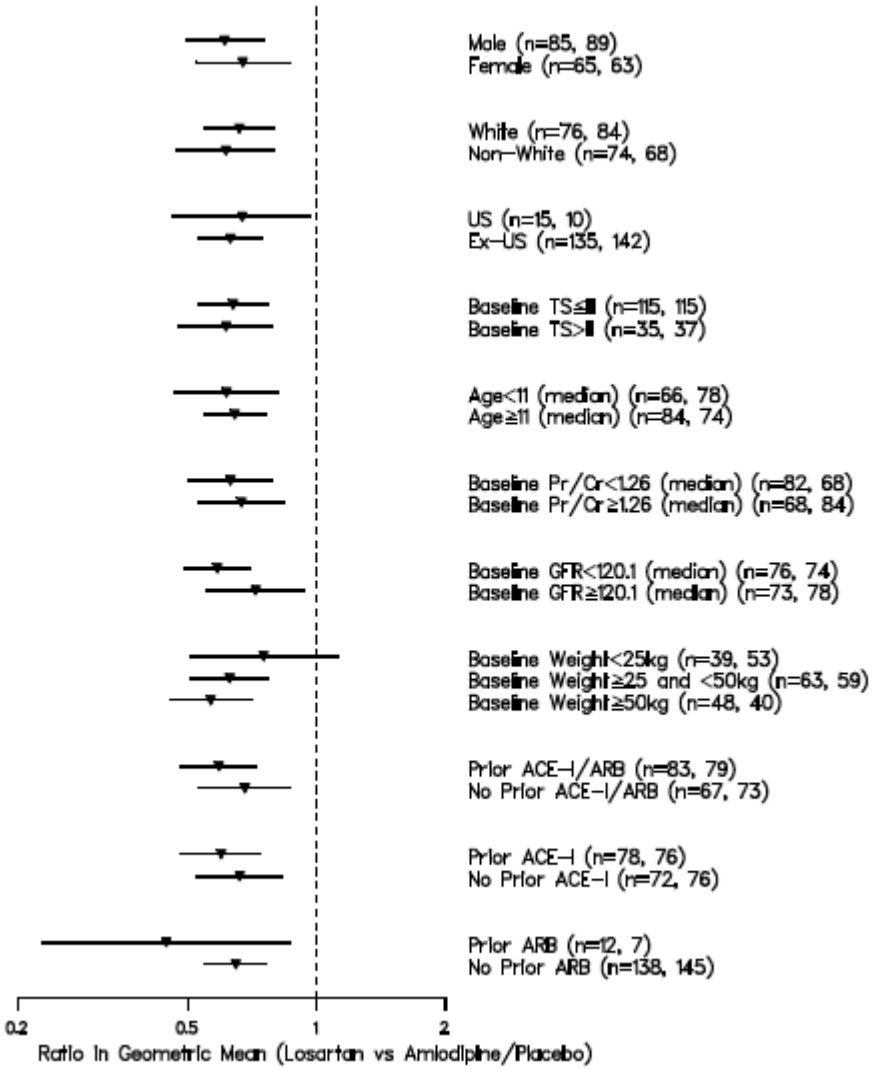

Figure 2: Proteinuria decline across different subgroups.

Table 3: Proteinuria decline in the normotensive group for age.

Treatment	N	Baseline GM (SD†)	Week 12 GM (SD†)	Pr/Cr (gm/gm) at Week 12	
				% Reduction‡ from Baseline (95% CI)	GM Ratio§ vs Control (95% CI)
Age: <median (10 years)					
Losartan	49	1.25 (2.71)	0.81 (3.19)	35.42 (16.96, 49.78)	0.63 (0.45, 0.88)
Placebo	64	1.50 (5.73)	1.51 (8.62)	-2.92 (-28.27, 17.42)	
Age: ≥median (10 years)					
Losartan	72	1.09 (1.67)	0.71 (1.76)	33.47 (24.59, 41.31)	0.65 (0.54, 0.78)
Placebo	58	1.50 (5.11)	1.52 (6.40)	-2.60 (-18.29, 11.00)	

† Based on log-normal distribution approximation.

‡ Derived as (1-exp(within-group LS-Mean))*100%.

§ Derived as exp(between-group LS-Mean).

LS-Mean derived from mixed model for change from baseline in Pr/Cr (on logarithmic scale) with terms for treatment, time, treatment by time, hypertensive status, prior ACE-I/ARB use and baseline.

GM = Geometric Mean.

Table 4: Proteinuria decline in the hypertensive group for age.

Treatment	N	Baseline GM (SD†)	Week 12 GM (SD†)	Pr/Cr (gm/gm) at Week 12	
				% Reduction‡ from Baseline (95% CI)	GM Ratio§ vs Control (95% CI)
Age: <median (13 years)					
Losartan	15	1.63 (1.58)	0.99 (1.57)	44.16 (23.27, 59.37)	0.64 (0.40, 1.03)
Amlodipine	12	2.14 (3.44)	2.24 (5.64)	12.96 (-23.05, 38.43)	
Age: ≥median (13 years)					
Losartan	14	2.28 (5.48)	1.60 (5.99)	42.15 (25.36, 55.16)	0.52 (0.38, 0.72)
Amlodipine	18	1.56 (2.42)	1.90 (3.23)	-10.46 (-37.72, 11.40)	

† Based on log-normal distribution approximation.

‡ Derived as (1-exp(within-group LS-Mean))*100%.

§ Derived as exp(between-group LS-Mean).

LS-Mean derived from mixed model for change from baseline in Pr/Cr (on logarithmic scale) with terms for treatment, time, treatment by time, hypertensive status, prior ACE-I/ARB use and baseline.

GM = Geometric Mean.

Among the total study population, the normotensive stratum and the hypertensive stratum, respectively, the magnitudes of proteinuria reduction within these etiologies in study PN 326 were also consistent with that seen in the primary analysis of the total study population.

Comments RMS

It can be concluded that the data support the findings that short-term proteinuria decline was found across both age strata. The study was indeed not powered for an analysis according to etiology, although we can agree that short-term reduction in proteinuria was observed across all different etiologies.

Antihypertensive agents reduce blood pressure and protein excretion and slow the progression of renal disease. In hypertensive patients protein excretion is reduced by reducing blood pressure to target levels (130/80 mmHg) in adults when protein excretion is >1g/day. Therefore, it is very important to exclude blood pressure dependent decline in proteinuria to define the decline in proteinuria beyond blood pressure decline only.

As expected in the normotensive patients, blood pressure was reduced more in the losartan group than in the placebo group. The MAH's conclusion that the observed BP reduction may at least in part have contributed to the observed reductions in proteinuria is shared. The proposed SPC changes in section 4.2 and 5.1 are in line with this observation and of such relevance that it is acceptable to include this information in the SmPC. In addition, in these patients with a different renal disease etiology, it is not known whether proteinuria is an appropriate efficacy marker, specifically in the normotensive group. No long-term data are available in this population. This raises the question whether normotensive pediatric patients will benefit from BP lowering therapy even though a short-term decline in proteinuria was demonstrated. At the moment, losartan is also not indicated for treatment of normotensive adult patients with proteinuria.

Supportive studies

The MAH has previously conducted 2 clinical trials using losartan in paediatric hypertension in 2000-2001.
Protocol 225 was a pharmacokinetic study that examined 50 hypertensive children ages 1 month to 16 years. The pharmacokinetics of losartan and the active metabolite, were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.
Protocol 227 was an open-label dose-response study conducted in 177 hypertensive children 6 to 16 years of age. Patients weighing 20 kg to < 50 kg received doses of 2.5 mg, 25 mg, or 50 mg once daily while patients weighing 50 kg or greater received doses of 5 mg, 50 mg, or 100 mg once daily. The results showed that losartan reduced trough blood pressure in a dose-dependent manner. However, the lowest doses studied, 2.5 mg, and 5 mg, corresponding to an average daily dose of approximately 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy.

Clinical studies in special populations
This application considers evaluation of treatment of children and adolescents up to 17 years.

Analysis performed across trials (pooled analyses and meta-analysis)
No submitted data.

III.3.3 Clinical safety

Patient exposure

The number of patients who took losartan in tablet form at any dose was 110, while 46 patients took losartan suspension. Eighteen patients took losartan tablet at > 1.75 mg/kg/day for at least one day during the double-blind period. Two patients on losartan suspension were on a dose of > 1.75 mg/kg/day.

The MAH has also conducted 2 previous studies of losartan in children aged 1 month to 16 years, in which the safety and tolerability data appeared to be similar to that seen in the adult population.

Comments RMS
Previously no safety issues appeared in children and adolescents. However, patient numbers were small and one study was open-label. Therefore the currently submitted – much larger - study is considered critical in defining the safety profile for patients <18 years. Also post-marketing data can contribute to the safety evaluation.

Adverse events

Pivotal study

Table 5: Number of adverse events.

	Losartan (N=152)		Amlodipine/Placebo (N=154)		Difference in Percentages Losartan vs Amlodipine/Placebo	
	n	(%)	n	(%)	Estimated	(95% CI)†
Patients in population	152		154			
with one or more adverse events	93	(61.2)	85	(55.2)	5.99	(-5.1, 16.9)
with no adverse event	59	(38.8)	69	(44.8)		
with drug-related‡ adverse events	8	(5.3)	8	(5.2)	0.07	(-5.3, 5.5)
with serious adverse events	7	(4.6)	5	(3.2)	1.36	(-3.4, 6.4)
with serious drug-related adverse events	0	(0.0)	2	(1.3)	-1.30	(-4.6, 1.2)
who died	0	(0.0)	0	(0.0)		
discontinued§ due to an adverse events	1	(0.7)	6	(3.9)	-3.24	(-7.7, 0.2)
discontinued due to a drug-related adverse event	0	(0.0)	3	(1.9)		
discontinued due to a serious adverse event	1	(0.7)	2	(1.3)		
discontinued due to a serious drug-related adverse event	0	(0.0)	2	(1.3)		

† Based on Miettinen-Nurminen method.
‡ Determined by the investigator to be related to the drug.
§ Study medication withdrawn.

Non-hypertensives:
Of 246 patients (122 on losartan and 124 on placebo), 77 patients (63%) in the losartan group and 69 (56%) in the placebo group had 1 or more clinical AEs; 5 in each group were deemed drug-related.

Hypertensives:
Of 60 patients, the losartan and amlodipine groups each had 16 patients with 1 or more clinical AEs; 3 in each group were drug-related.

Expected adverse events in this study were pre-defined as angioedema, hyperkalemia, renal dysfunction and hypotension. The incidence was small during the 12-week treatment period. There was 1 (0.66%)

report of hypotension on losartan (non-hypertensive stratum), which was considered drug-related. Five cases of renal dysfunction were reported: 2 (1.32%) on losartan (hypertensive stratum), 1 of which was considered drug-related; 1 (0.66%) on placebo, also considered drug-related; and 2 (1.32%) in the amlodipine group, which were not drug-related. There was 1 report of non-drug-related hyperkalemia that occurred at the end of the 4-week run-in period, on the day of randomization before study drug (losartan) was started. No significant differences in ECIs were seen between the 2 groups.

Comments RMS
The reported AEs during the pivotal study do not deviate from adverse effects already mentioned in the SPC for adults. However, in the normotensive stratum, one patient experienced a hypotensive adverse event. This is considered a potential problem in treatment of normotensive patients with antihypertensive therapy. It is agreed with the MAH that regular blood pressure monitoring is required and should be standard care in patients treated with antihypertensives. The statement as proposed in the amended SPC in section 5.1 is considered sufficient.

Serious adverse events and deaths

Pivotal trial

Non-hypertensives:
There were 5 serious clinical AEs (gastroenteritis, lung metastases, bronchitis, bacterial peritonitis and hydronephrosis) in the losartan group, none of which was considered drug-related. The placebo group had 5 serious clinical AEs (proteinuria, bronchitis, 2 cases of urinary tract infection and rash), 2 of which were drug-related. No one on losartan discontinued as a result of a clinical AE. In the placebo group, 4 discontinued from clinical AEs: 2 patients from drug-related AEs (nephrotic syndrome, tracheobronchitis and tonsillitis); and 2 from drug-related SAEs,

Hypertensives:
The losartan group had 2 serious AEs (varicella and systemic lupus erythematosus in 1 patient with a history of systemic lupus erythematosus), none of which was considered drug-related, There were no serious AEs in the amlodipine group. No serious laboratory AEs occurred. On losartan, 1 patient discontinued from a SAE (lymphoma), which was not considered drug-related.

Post-marketing
A total of 66 reports were identified. Thirty-six (55%) reports were serious and 30 reports (45%) were non-serious. Patient age groups were: neonates (2 reports), infant/toddler (15), child (27), and adolescent (22); there were 39 males and 21 females. The most frequently reported serious adverse experiences were overdose (17 reports), and acute renal failure (7). The majority of the reports of acute renal failure noted underlying comorbidities and/or concomitant medications that may have contributed.

Comments RMS
The serious adverse events are not considered unexpected. These events do not alter the safety profile of losartan.

Laboratory findings, vital signs

Non-hypertensives
7 patients on losartan versus 12 on placebo had 1 or more laboratory AEs; none in the losartan group and 3 in the placebo group were considered drug-related. No serious laboratory AEs occurred.

Hypertensives
One patient on losartan and none on amlodipine had 1 or more laboratory AEs; there were no drug-related laboratory AEs.

No significant difference in GFR change over the 12 weeks was seen between losartan and amlodipine/placebo.

Comments RMS
The submitted report of vital signs is considered satisfactory. Probably no further decline in GFR is seen in both losartan and amlodipine/placebo treated patients because GFR remains similar during these 12 weeks. However, 12 weeks is considered too short to really draw conclusions on maintaining renal function.

III.4 Pharmacovigilance System

The Applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version: 5, Dated: 22 August 2008).
The Pharmacovigilance system as is currently described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

III.5 Risk Management Plan

Within the submitted dossier a Risk Management Plan (RMP version 1.0, dated 18 November 2008) are provided.

The MAH has provided study synopsis for the ongoing and planned clinical trials. No pharmacoepidemiological studies are currently ongoing or planned. There are 3 studies ongoing (extension of P326, P948), and one study is proposed (P337).

Actions	Milestones/Exposure	Milestones/Calendar Time	Study Status
Clinical Study: Protocol 326	P326 Losartan in Pediatric Proteinuria (Open Label Extension): n= 259 patients	First Patient Entered extension: September 2007 Completion: June 2011 Results Available: (projected) September 2011	Ongoing
Clinical Study: Protocol 337	P 337 Losartan in Pediatric Hypertension	First Patient will be Entered: December 2008 Completion: December 2010 Results available (projected): April 2011	Planned
Clinical Study: Protocol 948	P 948 HEAAL (Heart failure Endpoint evaluation with the Angiotensin II Antagonist Losartan)	First Patient Entered: November 2001 Completion: March 2009 Results Available: December 2009	Ongoing
Enhanced Pharmacovigilance Reporting of Postmarketing Adverse Events in Pediatric Patients	PSURs will be provided every 6 months for 2 years	Begins with the next PSUR period (02 Sep 2008 to 01 Mar 2009), and concludes with the period 02 Mar 2010 to 01 Sep 2010 (PSUR submission date October 2010).	Planned

Summary of the Risk Management Plan
The proposed RMP for losartan considers that the planned activities for the safety concerns are generally covered by routine pharmacovigilance activities, namely text in relevant label sections, continued surveillance of all spontaneously reported cases; continued surveillance of concerned events reported in the ongoing and planned open-label trials.
No additional risk minimisation activities are warranted beyond those described in the pharmacovigilance plan and included in the product information.

Conclusions
Assessment of Risk Management Plan led to the following conclusions:
- Routine pharmacovigilance activities are considered adequate for this product. No additional measures are currently deemed necessary.

Further, the member states have made the following comments:
- In study P948, a sample size is proposed of 3,240 patients. From the data that are submitted, we are not sure whether this number is sufficient. The MAH is invited to comment at the time of the next PSUR submission.
- In study P948, the applicant assumes that there will be no loss to follow-up in the two treatment groups. It is doubtful whether this is realistic. The MAH is invited to comment at the time of the next PSUR submission.
- In the timelines for the ongoing and proposed studies, no interim analyses are mentioned. However, in the synopsis of study P948, an adjustment is made for interim analyses. The MAH should include the timelines for interim analyses in the table that is presented in section 2.6 of the RMP and submit this updated RMP at the time of the next PSUR submission.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Benefit
The MAH has conducted a study in children and adolescents to evaluate the effects of losartan on reduction of proteinuria. Losartan was compared to placebo (for normotensives) and amlodipine (for hypertensives). The design of the study submitted to evaluate the effect of losartan in the hypertensive patients was considered appropriate. A comparison was made to amlodipine for the hypertensive patients to allow for an evaluation of the decline in proteinuria beyond blood pressure control. Blood pressure reduction in hypertensives is shown to reduce proteinuria. However, the study was not able to demonstrate this, as on losartan treatment blood pressure was reduced considerably more than on amlodipine treatment (approximately 5mmHg difference). The observed blood pressure reduction may have contributed, at least partly, to the observed reduction in proteinuria.

In the normotensive pediatric patients it is questionable whether these patients will benefit from BP lowering therapy even though a short-term decline in proteinuria was demonstrated. First, the group of normotensive patients has probably a different etiology for their renal disease, and it is therefore not known if proteinuria is the proper risk marker for predicting long term outcome. An additional problem is that, in adults, losartan is currently not indicated to treat normotensive patients with proteinuria. Although it is in conflict with the currently approved indication for adults, this information is of such relevance that it is accepted to include it in section 5.1 of the SmPC.

Risk
This study is considered pivotal in defining safety as it is a placebo-controlled double-blind study, while a previous study was open-label. In addition, post marketing results could also contribute to the safety profile evaluation. The study, in general, did not raise major safety concerns to the treatment of losartan in children and adolescents. No unexpected severe adverse events were noticed which would question the safety profile of losartan. However, hypotension is considered one of the major safety concerns which could be associated with losartan when normotensive patients are treated. Indeed, in this safety evaluation one patient was found with a hypotensive drug reaction on losartan. A remarkable result is that, based on the results of the Glomerular Filtration Rate (GFR), no differences were found in the development of kidney disease in active and control groups. However, 12 weeks might be too short for a proper evaluation. Also long-term hard clinical endpoints are not evaluated. The 3 years extension study should give more insight.

Benefit/risk
With the provided data, a clear benefit of losartan on decline in proteinuria in hypertensive children and adolescents with proteinuria of different etiology up to 17 years old has not been demonstrated. Assessment of the provided study is hampered as the control group chosen in the hypertensive stratum

seems suboptimal. For the normotensive stratum, it is questionable what will be the exact (long-term) benefit for these paediatric patients due to the different etiology from adults, which questions if proteinuria is the proper risk marker for predicting long term outcome. In addition, losartan is currently not indicated in normotensive patients with proteinuria. Although it is in conflict with the currently approved indication for adults, this information is of such relevance that it is accepted to include it in section 5.1 of the SmPC.

Overall conclusion
Agreement between member states was reached during a written procedure. The type II variation was finished on 6 April 2009.

The MAH intends to submit a request for a reward in the form of a 6-month extension of the supplementary protection certificate.

The following statement should be included in the marketing authorisation of Cozaar 12.5 mg, 50 mg and 100 mg film-coated tablets:

"The development of this product has complied with all measures in the agreed paediatric investigation plan P/9/2008. For the purpose of the application of Article 45(3) of Regulation EC (No) 1901/2006, all studies in the agreed paediatric investigation plan P/9/2008 were completed after the entry into force of that Regulation.
The Summary of Product Characteristics reflects the results of studies conducted in compliance with this agreed paediatric investigation plan."

V Summary of Product Characteristics (SPC)

4.1 Therapeutic indications
Treatment of essential hypertension in adults and in children and adolescents 6 - 18 years of age.

The MAH alignes the text in section 4.1 with the recently approved text of the Commission Decision on the Article 29 referral, procedure number EMEA/H/A-29-PAD/1022 (decision dated 22 January 2009) to ensure consistency of the product information.

4.2 Posology and method of administration

Use in paediatric patients
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-18 years old for the treatment of hypertension (see 5.1: Pharmacodynamic properties). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 : Pharmacokinetic properties).

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in paediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m2, as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

5.1 Pharmacodynamic properties

Paediatric population
Paediatric Hypertension
The antihypertensive effect of COZAAR was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filration rate > 30 ml/ min/ 1.73 m2. Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

Long-term effects of losartan on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥0.3. The hypertensive patients (ages 6 through 18 years) were randomized to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomized to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group (p≤0.001). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9;-51.1) versus +2.4% (95% CI -22.2;14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mm Hg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mm Hg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group. Long-term effects of reduction of proteinuria in children have not been studied.

ANNEX II – Type II variation NL/H/1457/004/II/004

I Recommendation

Based on the review of the data on safety and efficacy, the RMS considers that the variation application for Cozaar ® 2.5 mg/ml to section 4.1, 4.2 and 5.1 of the SPC is approvable.

II Executive Summary

II.1 Scope of the variation

The MAH submitted a type II variation for Cozaar® tablets for paediatric patients via the MRP. The application concerns changes proposed to the SPC in section 4.2 and 5.1, to extend the information for treatment of proteinuria to a paediatric patient population with renal disease. To support these changes one pivotal study was submitted. The pivotal study included children aged 1 to 17 years with proteinuria from a wide range of etiologies. The objectives and design of the study were discussed in CHMP scientific advice and agreed upon with the Paediatric Committee (PDCO) in the Paediatric Investigational Plan. In addition to this study, the MAH is further studying paediatric hypertension development in lower age groups through a dose ranging trial (P337) in hypertensive children 6 months to 6 years old. The type II variation for the tablets (NL/H/1457/001-003/II/002) was positively concluded on 4 April 2009.
With this variation (NL/H/1457/004/II/004) the MAH proposes to update the product information with paediatric data from study protocol 326 in order to align with the film-coated tablets. Changes are proposed to the SPC section 4.1, 4.2 and 5.1.

The MAH has submitted the dossier to the MEB and the CMSs involved in the MRP. Cozaar oral suspension is approved for the indications:

- *Treatment of essential hypertension in adults and in children and adolescents 6-16 years of age.*
- *Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.*
- *Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.*
- *Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).*

On 23 October 2008, the CHMP gave a positive opinion for a line-extension under Article 29 of the Paediatric Regulation (EC) 1901/2006 for Cozaar and associated names (losartan potassium), from Merck Sharp & Dohme BV, to add a paediatric formulation of powder and solvent for oral suspension. This was the first recommendation for a line-extension relating to a new pharmaceutical form for use in the paediatric population on the basis of data generated in accordance with an agreed paediatric investigation plan (PIP). The paediatric formulation has been developed for the treatment of essential hypertension in children and adolescents 6-16 years of age.
At 22 January 2009, the Commission Decision for the new paediatric formulation for Cozaar which was evaluated under Article 29 of the Paediatric Regulation was available. Based on this Decision national marketing authorisation for the Cozaar powder and solvent for oral suspension, to comply with the EC decision, were granted in the EU countries.

The national line-extension MAs for the oral suspension are included in the MRP with NL as RMS (NL/H/1457/004).

II.2 Supplementary paragraph

Losartan is an oral, specific, and selective angiotensin-II receptor (type AT1) antagonist. *In vitro* and *in vivo*, both 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 synthesis.
RAAS inhibitors are advocated as first choice antihypertensive drugs in patients with proteinuria and hypertension. In general in an adult population, one antihypertensive drug is not sufficient to reach blood pressure goals in these patients. The RENAAL and IDNT studies demonstrated that 3-4 antihypertensive drugs are needed in hypertensive patients with diabetic severe proteinuria to reach blood pressure targets. Losartan (and irbesartan) demonstrated to give additional decline in proteinuria beyond blood pressure control – in those with optimised antihypertensive therapy -, eventually resulting in a significant decline in the risk of need for renal transplantation or long-term dialysis. The benefit of treating normotensive adults with proteinuria has not been demonstrated. It has been suggested that excessive lowering of blood pressure is not advisable as renoprotection as a function of blood pressure lowering may present itself as a J-curve [1]. This means that a too low blood pressure target may be associated with a higher risk for cardiovascular disease and might also have a detrimental effect on kidney disease.

III Scientific discussion

III.1 Quality aspects

No new data have been submitted.

III.2 Non clinical aspects

No new data have been submitted.

III.3 Clinical aspects

No new data have been submitted. The submitted study was already evaluated in variation (NL/H/1457/001-003/II/002), see Annex I.

III.3.1 Clinical pharmacology

No new data have been submitted.

III.3.2 Clinical efficacy

No new data have been submitted. The submitted study was already evaluated in variation (NL/H/1457/001-003/II/002), see Annex I.

III.4 Pharmacovigilance System

No new data have been submitted. The submitted Pharmacovigilance system was already evaluated in variation (NL/H/1457/001-003/II/002), see Annex I.

III.5 Risk Management Plan

No new data have been submitted. The submitted Risk Management Plan was already evaluated in variation (NL/H/1457/001-003/II/002), see Annex I.

[1] Jafar et al. Ann. Intern Med. 2003 Aug 19; 139(4):244-52.

IV OVERALL CONCLUSION AND Benefit-risk assessment

As all submitted data were already evaluated in variation NL/H/1457/001-003/II/002, which was was positively concluded on 4 April 2009, this variation was considered approvable by the member states on 16 July 2009.

V Request for supplementary information as proposed by the Rapporteur

None.

VI Conditions for the approval of the type II variation as proposed by the Rapporteur

VI.1 Summary of Product Characteristics (SPC)

The proposed additions in the SPC can be accepted on the basis of the provided data.

VI.2 Package Leaflet

There are no changes proposed by the MAH.

Annex III – Renewal Marketing Authorization

I Recommendation

Based on the review of the data on quality, safety, and efficacy the RMS considers that the Renewal for NL/H/1457/001-003/R/001 Cozaar 12.5 mg, 50 mg, and 100 mg film-coated tablets is approvable for unlimited time.

II Scope

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

- Nine PSURs covering the period 02 Sep 2004 to 01 Mar 2009 and a Summary Bridging report (*ref. 1994*) covering the same period, dated 16 Mar 2009.
- The Worldwide Product Circular (*WPC-CZR-T-122008, dated 12 Dec 2008*) is the CCDS is used as Reference Safety Information
- Approved SPC/MRP text in English (*EUSPC-CZR-T-042009/Final for Variation NL/H/1457/001-003/II/002, version 16 April 2009*)). This SPC also includes the CHMP revisions from Art 29 line extension to register a new oral formulation, as applicable to the tablets (CHMP opinion date Oct 23. 2008). The MAH stated that no changes are being proposed with this renewal.
- Clinical expert statement dated 15 April 2009 (not signed).
- Quality expert statement dated 08 April 2009 and signed.
- Stability data for the tablets packed in blisters and bottles. These stability data were also submitted during the type II variation NL/H/1457/001-003/II/001, Update Module 3 and the repeat use MRP NL/H/1457/001-003/E/001, therefore these data are not assessed again.

The SBR (Summary Bridging Report) including PSURs covering 02 Sep 2007 until 01Mar 2009 (*ref. 1986, 1988* and *1993*), the clinical expert statement and section 4.8 of the SPC proposal are assessed in this assessment report.

The proposed common renewal date is 31 December 2009.

Assessment led to several remarks (see preliminary renewal assessment report dated 6 July 2009). Comments were received comments from Romania, Germany and Ireland and a notification was received from United Kingdom, France, Latvia and Poland that they have no comments.

III Summary of authorities comments and MAH's response

- The MAH has comfirmed that the current SPC, approved with variation II/003, is in line with the most recent company core safety information with the exception of section 4.9 of the SPC, overdose. The MAH proposed to revise the overdose text for accuracy and consistency with the current Company Core Data Sheet for COZAAR. The following amendments were made to section 4.9 (corrections in red):

4.9 Overdose

Symptoms of intoxication
~~No case of overdose has been reported.~~ Limited data are available with regard to overdose in humans. The most likely ~~symptoms~~ manifestation of overdose would be ~~depending on the extent of overdose~~, are hypotension~~,~~ and tachycardia, ~~possibly.~~ B~~b~~radycardia could occur from parasympathetic (vagal) stimulation.

Treatment of intoxication
If symptomatic hypotension should occur, supportive treatment should be instituted.
Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilisation of the cardiovascular system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither losartan nor the active metabolite can be removed by haemodialysis.

- The name of excipient *hydroxypropyl cellulose* has been changed in to *hyprolose*.

- Losartan takes part in the PSUR synchronisation project. An EU Harmonised Birth Date of 2 September 1994 has been agreed upon (FI/H/PSUR/0001/001). In order to participate in the project the next PSUR should have a data lock point of September 2010. The MAH was therefore advised to participate in this project and to adhere to the proposed PSUR cycle.
  It is the MAH's intention to participate in the work sharing initiative which is led by the pRMS Finland. In addition, the MAH will be submitting PSURs on a 6-monthly schedule due to the recent approval of the paediatric data for losartan and as agreed during the art 29 referral (EMEA/H/A/-29 PAD/1022). The next paediatric PSUR will be submitted in October 2009 and the assessment will be led by the RMS the Netherlands.

IV Conclusions

All the issues are resolved. The renewal may be granted for an unlimited period. The renewal date is 31 December 2009.

The next PSUR will be submitted within 60 days from the DLP, using the allocated data lock point (DLP) of September 2010.

The renewal procedure ended positively on 9 November 2009.

LIST OF ABBREVIATIONS USED IN ANNEXES

ACE-I	Angiotensin Converting Enzyme Inhibitor
AE	Adverse event
ARB	Angiotensin Receptor Blocker
DBP	Diastolic Blood Pressure
GFR	Glomerular Filtration Rate
PDCO	Paediatric Committee
Pr/Cr ratio	Protein/Creatinine ratio
RAAS	Renine Angiotensine Aldosteron System
SBP	Systolic Blood Pressure
SBR	Summary Bridging Report
T2DM	Type 2 Diabetes Mellitus