# Assessment Report of Co-Rapporteur European Paediatric Worksharing project

## COZAAR
## (Losartan)

## Marketing Authorisation Holder: Merck Sharp & Dohme

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| **Rapporteur** | **DE** |
| **Co-Rapporteur** | **UK** |
| **Paediatric assessment Procedure start date:** | **03/04/07** |
| **Deadline for Rapporteurs' Reports:** | **12/06/07** |
| **Deadline for members States comments:** | **27/06/07** |
| **Date of this report:** | **12/06/2007** |

# ADMINISTRATIVE INFORMATION

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| Currently approved indications: | *Hypertension*<br>'Cozaar' is indicated for the treatment of hypertension.<br><br>*Hypertensive patients with left ventricular hypertrophy*<br>In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of 'Cozaar' for this indication in black patients (see section 4.4 'Special warnings and Precautions for Use-*Race'* and section 5.1 Pharmacodynamic Properties, LIFE study, *Race*).<br><br>*Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*<br>'Cozaar' is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria. |
| Pharmaceutical forms affected by this application: | COZAAR Film Coated Tablets |
| Strengths affected by this application: | COZAAR 100 mg Film Coated Tablets<br>COZAAR 50 mg Film Coated Tablets<br>COZAAR 25 mg Film Coated Tablets |

# I. EXECUTIVE SUMMARY

## Introduction

Losartan is an angiotensin-II receptor (type AT1) antagonist. The data provided to support paediatric exclusivity in the US have previously been considered in the UK as a national procedure and the UK SmPC amended following a subsequent national variation procedure on 14th November 2005. This clinical assessment for the EU Worksharing procedure is essentially that previously performed by the UK for the national procedure in 2004, but those new data which have been presented for the first time in this dossier (i.e. the Addendum 01 May 2004 – 30 April 2006 and the new publications) have been assessed in addition.

The Clinical Expert Overview is by Merck and Co Inc, Rahway, New Jersey, USA. The proposal in this document that, as the available data are limited to those aged more than 1 month and that no patients with hepatic impairment were included in the trials, that no dosing recommendations will be included for those aged <1 month of age and in children with hepatic impairment, appears reasonable and is endorsed.

The MAH has submitted the results from two studies in hypertensive children one investigating the effect of losartan on pharmacokinetic parameters (Study 225) and one a dose ranging trial on blood pressure in hypertensive children (Study 227). In addition a bioequivalence study in adults has been presented comparing an unlicensed suspension formulation with the tablet formulation (Study 216). Other relevant clinical data include a Clinical Overview, 2 recent publications and a Cumulative Safety Review with an addendum for the recent period 01 May 2004 – 30 April 2006.

- ***Pharmacokinetics***

    - Study 225

The pharmacokinetics of losartan and the metabolite E-3174 appear comparable in the four age groups that were examined. Differences in some parameters were statistically significant, especially for E-3174, when pre-school children were compared with adolescents, but the differences are not considered to be clinically important. The active metabolite E-3174 was formed from losartan in all age groups studied.
Based on historical data, it appears that the pharmacokinetic parameters of losartan and E-3174 in paediatric patients in this study are generally comparable to those in adults. No information has been presented on children with severe renal impairment, as patients with GFR <30mL/min/1.73m$^2$ were excluded from the trial; nor are there are data in children with hepatic impairment.
These pk data are considered to be of value to prescribers and hence the assessor recommends that the EU SmPCs should be modified to include a summary of study 225 in Section 5.2. In addition, the assessor recommends that SmPC Section 4.2 should be modified to include a statement that use is not recommended in children with a GFR <30mL/min/1.73m$^2$ (as no data exist in this group) and also to include a statement that use is not recommended in children with hepatic impairment.

    - Study 216

The suspension used in the study has not been demonstrated to be bioequivalent with the tablet formulation used. The issues of the similarity of this suspension to that proposed for extemporaneous manufacture and the reproducibility of the extemporaneous suspension and the availability in the EU of the excipients *OraSweet* and *OraPlus* are discussed in the

pharmaceutical report, and there are concerns in this area. The exact suspension formulation used may have a significant influence on bioavailability. Thus, results generated using this suspension cannot necessarily be applied to any other suspension using different suspending agents. There are therefore issues surrounding the pharmacokinetics of the formulations used in these studies with respect to the extrapolation of the data to the European setting.

The 12.5 mg tablet used is not currently licensed in the UK and other EU Member States. It would be a useful strength for paediatric use and consequently the assessor recommends that the MAH should be urged to obtain an MA for this throughout the EU as soon as practicable. In addition, a suspension formulation which is bioequivalent with tablet formulations would be useful for paediatric use and consequently the assessor recommends that the MAH should be urged to develop such a formulation for paediatric use and to obtain an MA for it in the EU as soon as practicable.

- ***Efficacy***

    - Study 227

The results showed a significant blood pressure lowering effect of losartan in hypertensive children in doses equal or higher than 25 or 50 mg/day for patients weighing both <50 kg and ≥50 kg respectively. The lowest dose (2.5/5mg) had no useful efficacy. The fact that no other doses between 2.5/5mg and 25/50mg were tested does not allow the conclusion to be drawn that the 25/50mg is the lowest effective dose. Nevertheless, the limited data provided support the contention that losartan is an effective treatment for hypertension in the paediatric population and this finding should therefore, in the view of the assessor, be reflected in the EU SmPCs.
The SmPC should therefore be modified to include a summary of study 227 in Section 5.1. Section 4.2 should be amended to include posology advice for the paediatric population. Statements should be included that the efficacy data are limited, and that as no data exist in those aged <1 month of age, use cannot be recommended in these individuals.

- ***Safety***

Data are limited both in terms of the number of patients exposed to the drug and the length of exposure, but suggest that losartan is well tolerated in children. Reported events were often related to renal impairment or liver function abnormalities which are currently already "labelled" for Cozaar. The information provided raises no significant concerns of any increased risk for children compared to adults. There is no information on the drug effects in patients with severe renal or hepatic impairment; therefore, as stated above, the assessor recommends that the SmPC should state that the drug should not be used in children with these conditions. There are no long term safety data in children to provide reassurance that losartan has no effect on growth or puberty, and no long term efficacy data to provide reassurance that the drug has a beneficial effect in reducing cardiovascular morbidity and mortality. The SmPC should be amended to state this.

In conclusion, in the light of the presented data, the following safety statements should be included in the SmPC as an aid to prescribers:-

- **Section 4.2 Posology and method of administration**

Use in children and adolescents:
-Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available.
-Losartan is not recommended in children with hepatic impairment.

- **Section 4.8 Undesirable effects**

Data in children are limited. However, the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

- **Section 5.1 Pharmacological Properties**

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

No SmPC change is recommended as a consequence of consideration of the new publications.

# II. RECOMMENDATIONS

1. The Rapporteur recommends that as significant supportive data and experience now exists in the paediatric population that the SmPC for Cozaar should be modified to summarise these data.

In particular:-

1.1 Section 4.2 (posology and method of administration) should be modified to include dosing advice for children and adolescents, as follows:-

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients 20 to <50 kg, and 50 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 50 mg daily in patients weighing 20 to <50 kg, and 100 mg in patients ≥50 kg. together with the following caveats:-

1.1.1 A statement should be included that there are limited data on efficacy, safety and pharmacokinetics in hypertensive children and adolescents.
1.1.2 A statement should be included that Losartan is not recommended for use in neonates aged < 1 month of age as no data exist in these patients.
1.1.3. A statement should be included that losartan is not recommended for use in neonates and in children with glomerular filtration rate <30 ml/min/1.73 $m^2$, as no data are available in these patient groups.
1.1.4. A statement should be included that Losartan is not recommended in children with hepatic impairment.

1.2 Section 4.8 (Undesirable effects).
A statement should be included that data in children are limited. However, the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

1.3 Section 5.1 (Pharmacological Properties).

1.3.1 A summary of study 227 should be included in this Section.
1.3.2 A statement should be included that the long-term effects of losartan on growth, puberty and general development have not been studied.
1.3.3 A statement should be included that the long-term efficacy of losartan therapy in childhood to reduce cardiovascular morbidity and mortality has not been established.

1.4 Section 5.2 (Pharmacokinetic Properties).

A summary of study 225 should be included in this Section.

1.5 Other SmPC modifications should be made as listed in Annex 1 of this report.

2. The Patient Information Leaflet should be modified in line with the proposed SmPC changes.

3. The assessment report should be published on the HOA webpage.

4. As the 12.5 mg tablet is considered to be a useful strength for paediatric use, the MAH is encouraged is to obtain an MA for this product throughout the EU as soon as practicable.

5. A suspension formulation which is bioequivalent with tablet formulations is considered to be a useful product for paediatric use. Therefore the MAH is encouraged is to obtain an MA for such a product throughout the EU as soon as practicable.

# III. RAPPORTEUR'S ASSESSMENT REPORT

## III.1 Background

**Introduction.**

The forthcoming EU legislation on medicines for paediatric use has recently been finalised. Prior to its completion, the Mutual Recognition Facilitation Group (MRFG) agreed a procedure (the European Worksharing Project) to enable an increase in the amount of information included in the SmPCs for medicines licensed in the EU in respect of their paediatric use, as an aid for prescribers. In particular, the MRFG decided to obtain and review the paediatric data from all companies whose products appear on the United States Food and Drug administration (FDA) Paediatric Exclusivity Granted List. This is a list of active substances (with relevant sponsors) for which the FDA has granted data exclusivity in return for the submission of paediatric studies carried out in compliance with an FDA written request. For these products, paediatric data are known to exist.

As a consequence, the MA holder for *Cozaar* (MSD), was contacted by the regulatory authority of the Netherlands in May 2006. MSD were requested to submit all completed paediatric studies for *Cozaar* as well as a cumulative review of safety to all EU Member States, Norway, Iceland and Liechtenstein in line with the European Worksharing Project outlined above. For this procedure, DE was appointed Rapporteur and the UK Co-Rapporteur for the assessment.

Before the European wide procedure was initiated, the UK had previously considered the FDA Paediatric exclusivity data for *Cozaar* (losartan) as a national procedure. The data were considered by the Paediatric Working Group of the UK's Committee on Safety of Medicines on 14th December 2004 and a copy of the assessment report has been placed on the MHRA's website at :-

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=132

The UK national procedure concluded that:-

1. The company should be submitting a variation to amend the summary of product characteristics (SmPC) as follows:

***Section 4.2 (Posology and method of administration)***

The following text should be inserted:-

*Use in children and adolescents.*
*-There are limited data on efficacy, safety and pharmacokinetics in hypertensive children and adolescents aged 6-16 years (see sections 5.1 'Pharmacodynamic properties' and 5.2 'Pharmacokinetic properties'.*
*-For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients 20 to <50 kg, and 50 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 50 mg daily in patients weighing 20 to <50 kg, and 100 mg in patients ≥50 kg.*
*-Losartan is not recommended in neonates and in children with glomerular filtration rate <30 ml/min/1.73 $m^2$, as no data are available.*
*-Losartan is also not recommended in children with hepatic impairment.*

***Section 5.1 (pharmacodynamic properties) and 5.2 (pharmacokinetics)***

These sections should be amended with brief details of the efficacy and pharmacokinetic studies. The following text should also be added to section 5.1:

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

2. The patient information leaflet should be modified in line with the proposed SPC changes.

3. The assessment report should be published on the MHRA webpage.

In addition the applicant was strongly urged to develop a suspension form that could be licensed in the UK and also should make the 12.5mg tablet strength available.

The MA Holder subsequently submitted a variation application in the UK to amend the product particulars. This application was approved on 14th November 2005. The approved text incorporated into the UK SmPC was in line with the above conclusions but included additional text. The relevant text was as follows:-

**4.2 Posology and method of administration**

*Use in children and adolescents:*
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 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. The dose can be increased to a maximum of 50 mg once daily. In

patients ≥50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.
Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

**4.4 Special warnings and precautions for use**
*Hypotension and electrolyte/fluid imbalance*
In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of 'Cozaar'.

**4.8 Undesirable effects**
The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

**5.1 Pharmacodynamic properties**
*Paediatric Hypertension*
The antihypertensive effect of 'Cozaar' was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight ≥ 20 kg and a glomerular filtration rate ≥ 30 ml/min/1.73$m^2$. Patients who weighed ≥ 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥ 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, 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. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, 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.

**5.2 Pharmacokinetic properties**
*Pharmacokinetics in paediatric patients*
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients> 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

**Losartan**

Losartan is an angiotensin-II receptor (type AT1) antagonist. Angiotensin II which is formed from angiotensin I in a reaction catalysed by angiotensin converting enzyme, is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland).

In adults, losartan is currently indicated for the treatment of hypertension (in hypertensive patients with left ventricular hypertrophy. It is also indicated to reduce the risk of stroke) and for renal protection in type 2 diabetic patients with nephropathy. Prior to the UK National procedure use in children was not recommended.

***Cozaar* and FDA Paediatric Exclusivity**

In their Written Request, the FDA requested data that would provide "guidance for the use of losartan potassium to reduce blood pressure in paediatric patients." These data were to be derived from a dose-ranging trial in hypertensive patients; pharmacokinetic trials in subjects from four paediatric age groups as follows: infants and toddlers, pre-school children, school - age children, and adolescents; and safety data from the dose-ranging trial, and open treatment extension period of that trial or other comparable database, with a summary of available information on the safety of the drug in paediatric patients.

In support of Paediatric Exclusivity, the Sponsor conducted 2 clinical trials in paediatric patients: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants (Protocol 225); and a double-blind, randomized dose – response study of losartan in children with hypertension (Protocol 227). Data from an open-label, 2-period crossover study conducted in healthy adults to determine the relative bioavailability of a losartan suspension and marketed Cozaar 50- mg tablets (Protocol 216) was also submitted.

Paediatric Exclusivity was granted for losartan on March 20, 2002. The procedure resulted in the following labelling changes in the US:

-A statement was included to indicate that antihypertensive effects were established in hypertensive patients 6-16 years of age. However, a statement was also included that losartan is not recommended for paediatric patients less than 6 years or with glomerular filtration rate < 30mL/min/1.73 $m^2$ due to lack of data.
-Information was included on pharmacokinetics and dosing in paediatric patients 6-16 years of age.
-A statement was included to the effect that no relevant differences exist between the adverse event (AE) profiles for paediatric patients compared to reported AEs for adults.
-Information was included on the preparation of an extemporaneous suspension for paediatric use.

**Data Presented for EU Worksharing procedure**

On 14th July 2005, the marketing authorisation holder (MSD) replied to the MRFG's letter attaching relevant data. In their submission the following electronic documents were included:-

1. Covering letter and previous e-mail correspondence.

2. I. Administrative documentation:
-Letter from MEB regarding EU procedure.
-Table of Contents
-Clinical Overview
-SmPC revisions proposed by MHRA in December 2004
-SmPC changes proposed by MAH in this procedure.
-Annotated SPC for *Cozaar* products
-SmPC Fragment for Section 4.2

3. II Clinical Trial documentation:-
-Study 225:-An open label study to investigate the pharmacokinetics of losartan in hypertensive children and infants.
-Study 227-A double – blind randomised dose – response study of losartan in children with hypertension.
-Study 216-An open label randomised two period cross – over study to determine the relative bioavailability of losartan 50mg suspension and losartan 50mg tablet administered orally as a single dose.

4. III. Publications:-
-Ref 1. Sh. Shahinfar et al A Double-Blind, Dose–Response Study of losartan in Hypertensive Children,. *AJH 2005; 18:183–190.*
-Ref 2. D.Ellis et al. Antihypertensive and Renoprotective Efficacy and Safety of Losartan; *AJH 2004; 17:928–935.*

5. IV. Cumulative Safety Review.
-Addendum 01 May 2004 – 30 April 2006.

6. V. Quality documentation for suspension formulation.

These presented data are largely those which were assessed by the MHRA and considered by its expert group in 2004. There are however additions to these previous data in respect of the cumulative safety review, the publications and the quality documentation. For the safety review, an addendum has been included for the period 01 May 2004 – 30 April 2006. The 2 publications listed above were also not previously considered by the MHRA during the 2004 national review, nor were some of the references to the quality documentation in respect of the extemporaneous manufacture of a suspension formulation.

This clinical assessment for the EU Worksharing procedure is therefore essentially that previously performed by the UK for the national procedure in 2004, but the new safety data (the Addendum 01 May 2004 – 30 April 2006) and the new publications have been assessed in addition in this report.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Quality aspects

See separate report.

## IV.2 Non-clinical aspects

No preclinical data was submitted.

## IV.3 Clinical aspects

### IV.3.1 Submitted Documents.

#### IV.3.1.1 Covering letter

The covering letter of 14th July 2006 from the MAH summarises the content of the submitted data. It also provides information on those data which were not available for the MHRA review in 2004 and which are therefore new. These are:

- Publications in Section III (in PDF 08)
- Safety review addendum (in PDF 09)
- References to quality data (in PDF 09)

The covering letter also has appended to it various e-mail communications between the MAH and MHRA.

**Assessor's Comment**
These documents are self explanatory and require no further assessment or comment.

#### IV.3.1.2 Clinical Expert Overview

The Clinical Expert Overview is by, Merck and Co Inc, Rahway, New Jersey, USA.

The Clinical Overview summarises the sequence of events and the data provided for the FDA Paediatric Exclusivity and that of the MHRA national review of these data.

With regard to pharmacokinetics, the Clinical Overview points out that a suspension formulation was considered important for use in younger children, and argues that study 216 demonstrated equivalence in bioavailability in adults between Losartan 50mg tablets and 50mg of a suspension formulation. With regard to Study 225, which was performed in children and which investigated kinetics in 50 hypertensive paediatric patients aged from >1 month to <16 years of age, the Overview states that this trial showed that the kinetics of losartan and its active metabolite (E-3174) were similar in the age groups studied and were consistent with previous data from adults.

With regard to dose – response and efficacy, the overview is of the opinion that in Study 227, which was undertaken in 177 hypertensive paediatric patients aged 6-16 years, trough blood pressure was lowered in a dose dependent fashion. However the lowest dose level (2.5mg in those weighing <50kg and in those weighing 5mg >50kg) did not result in clinically effective lowering of hypertension.

In respect of the safety of Losartan from the above studies and from the post - marketing experience, the Clinical Overview opines that the safety profile in paediatric patients is comparable to that in adults.

The Overview concludes that the data available provide useful safety and dosing information for physicians treating hypertensive children. It points out, however, that data are limited to those aged more than 1 month and that no patients with hepatic impairment were included. Therefore no dosing recommendation is proposed for these groups. No comment is made on any of the proposed SmPC modifications.

**Assessor's Comments**
The assessor concurs with the general view of the clinical expert that the data available provide useful safety and dosing information for physicians treating hypertensive children which should be incorporated into the SmPC. The proposal that as data are limited to those aged more than 1 month and that no patients with hepatic impairment were included that no dosing recommendations will be included for those aged < 1 month or those with hepatic impairment appears reasonable and is endorsed.

### IV.3.1.3 SmPC Revisions proposed by the MHRA following the National Procedure in December 2004

The MAH lists the SmPC revisions proposed by the MHRA following the national review as follows:

**4.2 Posology and method of administration**

*Use in children and adolescents:* There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 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. The dose can be increased to a maximum of 50 mg once daily. In patients >50 kg, the starting dose is 50 mg once daily. The dose can be adjusted to a maximum of 100 mg once daily.
-Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

**4.4 Special warnings and precautions for use**

In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of 'Cozaar'.

**4.8 Undesirable effects**

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

**5.1 Pharmacodynamic properties**

*Paediatric Hypertension*
The antihypertensive effect of 'Cozaar' was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73m2. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, 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. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in

patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, 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.

**5.2 Pharmacokinetic properties**

*Pharmacokinetics in paediatric patients*
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

In fact, as previously stated, this text is not that actually proposed by the MHRA following the review of Paediatric data in 2004, but is that finally agreed between the MAH and MHRA at the conclusion of a subsequent National type II variation to implement the recommendations of the 2004 assessment of paediatric data. This text was incorporated into the UK SmPC in November 2005.

### IV.3.1.4 SPC changes for this procedure

As part of this procedure, the MAH proposes the following changes to all European SmPCs:-

**4.2 Posology and method of administration.**

<u>*Use in children and adolescents:*</u> There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 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').

The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension (see *Preparation of Suspension*). Dosage should be adjusted according to blood pressure response. In patients >50 kg, the starting dose is 50 mg once daily. 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.

<u>Preparation of Suspension (for 200 mL of a 2.5 mg/mL suspension)</u>

Add 10 mL of Ph. Eur. Purified Water to a 240 mL amber polyethylene terephthalate (PET) bottle containing ten 50 mg COZAAR tablets. Immediately shake for at least 2 minutes. Let the concentrate stand for 1 hour and then shake for 1 minute to disperse the tablet contents. Separately prepare a 50/50 volumetric mixture of Ora-Plus *** and Ora-Sweet SF ***. Add 190 mL of the 50/50 Ora-Plus / Ora-Sweet SF mixture to the tablet and water slurry in the PET bottle and shake for 1 minute to disperse the ingredients. The suspension should be refrigerated at 2-8°C and can be stored for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.

Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.

**4.4 Special warnings and precautions for use.**

In paediatric patients who are intravascularly volume-depleted, these conditions should be corrected prior to administration of 'Cozaar'.

**4.8 Undesirable effects.**

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

**5.1 Pharmacodynamic properties**

*Paediatric Hypertension*

The antihypertensive effect of 'Cozaar' was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73m$^2$. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, 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. When patients were randomised to continue losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients on losartan at the two higher doses. However, 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.

**5.2 Pharmacokinetic properties.**

*Pharmacokinetics in paediatric patients*
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

The proposals relating to the clinical aspects (i.e. all the above proposed modifications with the exception of the text in Section 4.2 in respect of the "*Preparation of Suspension"* are discussed in this report and the changes proposed are summarised in Annex. The proposals in

respect of "*Preparation of Suspension"* are considered in the accompanying Pharmaceutical report.

### IV.3.2 Clinical Pharmacology

**Pharmacodynamics**

No pharmacodynamic data have been submitted.

**Pharmacokinetics**

Two studies of relevance have been submitted as follows.

1. Study 225 was an open-label, multicentre study to investigate the pharmacokinetics of losartan in hypertensive children and infants.

2. Study 216 was an open label randomised two period cross – over study to determine the relative bioavailability of 50mg of a losartan suspension and a losartan 50mg tablet administered orally as a single dose. It was performed in adults.

- **Study 225**

This was is an open-label, multi-centre study which aimed at investigating the steady state (Day 7) pharmacokinetics of losartan in hypertensive children aged 1 month to <16 years.

**Study objectives**

*Primary*

1) To estimate plasma pharmacokinetic parameters (AUC0-24hr, Cmax, Tmax, and half-life) of losartan and E-3174 in children aged 1 month to <16 years.
2) To evaluate the safety and tolerability of losartan in children aged 1 month to <16 years.

*Secondary*

To estimate the urinary recovery and renal clearance of losartan and E-3174 in children <16 years of age.

**Study population**

The study included male and female patients one month to <16 years of age with a documented history of hypertension. Patients were grouped by age as follows:

• Group I: infants and toddlers (1 to 24 months);
• Group II: preschool children (25 months to <6 years);
• Group III: school-age children (6 to <12 years);
• Group IV: adolescents (12 to <16 years).

Age was defined as having reached a respective birthday as of the day of the study drug dose. Patients were required to have a glomerular filtration rate (GFR) ≥30 mL/min/1.73m$^2$.

Patients with severe or symptomatic hypertension, heart failure, clinically significant neurological, respiratory, gastrointestinal, hepatobiliary, or haematological disease, as well as those with a history of uncorrected coarctation of the aorta, bilateral renal artery stenosis, or renal artery stenosis to a single kidney were excluded. Severely nephrotic patients not in remission were also excluded.

**Dosing and sample collection**

The dosages in this study ranged from approximately 0.5 to 1.0 mg/kg once daily for 7 days (See Table 1). The maximum dose was 50 mg once daily. By way of comparison, the adult starting dose (50 mg) in a 70-kg adult = 0.7 mg/kg.

**Table 1. Losartan dosing according to age and weight**

| | |
|---|---|
| Patients <6 years and older patients who could not swallow tablets | losartan suspension 0.7 mg/kg once daily |
| Patients 6 years and older weighing <25 kg | losartan 12.5mg tablets once daily |
| Patients 6 years and older weighing ≥25 kg but <50 kg | losartan 25mg tablets once daily |
| Patients 6 years and older weighing ≥50 kg | losartan 50mg tablets once daily |

Blood specimens for plasma losartan and the primary metabolite (E-3174) assay were collected prior to the first dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 32 to 36 hours following the Day 7 dose (except in children younger than 4 years, in whom the collections at hours 2 and 6 were optional).
Urine collections were performed in the intervals of hours 0 to 8, and 8 to 24 after the Day 7 dose (urine collections were optional in Group I patients and in older patients who were not toilet trained).

**Patient demographics and clinical characteristics**
In total 50 patients entered and completed the study. Patient demographics are shown in Company Table 2.

**Table 2. Patient demographics**

| **Group I**<br>1 to 24 months | | **Group II**<br>6 to <12 years | **Group III**<br>6 to <12 years | **Group IV**<br>12 to <16 years |
|---|---|---|---|---|
| **Total No. of Patients** | 11 | 13 | 12 | 14 |
| Males (n)<br>Actual age range | 8<br>3 to 23 mo | 8<br>2 to 5 yr | 8<br>6 to 11 yr | 9<br>12 to 15 yr |
| Females (n)<br>Actual age range | 3<br>10 to 23 mo | 5<br>2 to 5 yr | 4<br>7 to 8 yr | 5<br>12 to 15 yr |
| Caucasian (n)<br>Black (n)<br>Hispanic (n) | 8<br>1<br>2 | 7<br>2<br>4 | 4<br>5<br>3 | 8<br>5<br>1 |
| Weight range (kg) | 7 to 14 kg | 10 to 19 kg | 24 to 59 kg | 52 to 139 kg |
| **Patients included in PK analysis (n)** | 9 | 13 | 11 | 14 |
| Males (n)<br>Actual age range | 8<br>3 to 23 mo | 8<br>2 to 5 yr | 7<br>6 to 11 yr | 9<br>12 to 15 yr |
| Females (n)<br>Actual age range | 1<br>23 to 23 mo | 5<br>2 to 5 yr | 4<br>7 to 8 yr | 5<br>12 to 15 yr |
| Caucasian (n)<br>Black (n)<br>Hispanic (n) | 7<br>1<br>1 | 7<br>2<br>4 | 4<br>5<br>2 | 8<br>5<br>1 |
| Weight range (kg) | 7 to 14 kg | 10 to 19 kg | 24 to 59 kg | 52 to 139 kg |

Most patients were receiving antihypertensive medication prior to the study as follows (ACE inhibitors n=21, calcium channel blockers n=17, beta-blockers n=8, furosemide, n=1 and

hydrochlorothiazide n=1). Concomitant antihypertensive medications included amlodipine (n=1), atenolol (n=1), captopril (n=1), furosemide (n=1), isradipine (n=1), nifedipine (n=1), and propranolol (n=3).

Pharmacokinetic data were obtained from 47 patients whose demographics are also summarised in Table 2. Urine data analysis was possible in 30 patients. All 50 patients were included in the evaluation of safety.

**Results**

*A. Plasma Pharmacokinetics*

The following two tables (3 and 4) present the plasma pharmacokinetic parameters for losartan and E-3174 respectively.

**Table 3. Summary statistics for plasma pharmacokinetic parameters of losartan in the 4 groups**

| **Group I n=9** | | **Group II n=13** | **Group III n=11** | **Group IV n=14** |
|---|---|---|---|---|
| Mean age (year) | 1.14 | 3.66 | 8.96 | 14.75 |
| Mean dose (mg/kg) | 0.7 | 0.7 | 0.77 | 0.54 |
| Mean dose (mg) | 6.85 | 10.57† | 26.55 | 50.4 |
| Mean weight (kg) | 9.92 | 15.03 | 35.04 | 99.24 |
| **AUC0-24 hr observed (ng∗hr/mL)** | | | | |
| Geometric Mean | 244.5 | 314.5 † | 251 | 303.1 |
| 95% CI | (162.2, 368.4) | (238.8, 414.3) | (141.5, 445.5) | (253.4, 362.5) |
| **AUC0-24 hr per 0.7 mg/kg** | | | | |
| Geometric Mean | 246.1 | 305.2 | 232.6 | 405.4 |
| 95% CI | (168.4, 359.6) | (237.7, 391.9) | (134.7, 401.5) | (337.4, 487.1) |
| **Cmax observed (ng/mL)** | | | | |
| Geometric Mean | 66.6 | 89.8 † | 98.7 | 105.1 |
| 95% CI | (40.9, 108.4) | (58.9, 137.0) | (63.5, 153.4) | (71.1, 155.4) |
| **Cmax per 0.7 mg/kg** | | | | |
| Geometric Mean | 67 | 89.5 | 91.4 | 140.6 |
| 95% CI | (43.0, 104.4) | (61.9, 129.4) | (61.3, 136.5) | (98.6, 200.6) |
| **Tmax (hr)** | | | | |
| Median ‡ | 1.05 | 1.07 | 2.03 | 1.54 |
| 95% CI § | (0.78, 2.53) | (0.77, 2.53) | (1.00, 3.54) | (1.49, 2.03) |
| **Half-Life (hr)** | | | | |
| Harmonic Mean | 1.93 | 2.37 | 2.18 | 2.41 |
| 95% CI | (1.62, 2.38) | (1.99, 2.95) | (1.83, 2.70) | (2.02, 2.98) |

† n=12. Excludes AN 4051 who received 2.5-times the intended dose.
‡ Hodges-Lehmann estimate. § Distribution-free confidence interval. CI = Confidence interval.

**Table 4. Summary statistics for plasma pharmacokinetic parameters of E-3174 in the 4 patient groups**

| **Group I n=9** | | **Group II n=13** | **Group III n=11** | **Group IV n=14** |
|---|---|---|---|---|
| **AUC0-24 hr observed (ng∗hr/mL)** | | | | |
| Geometric Mean | 1456.5 | 950.9† | 1163.6 | 1589.9 |
| 95% CI | (988.5, 2146.2) | (679.7, 1330.2) | (819.5, 1652.3) | (1165.2, 2169.5) |
| **AUC0-24 hr per 0.7 mg/kg** | | | | |
| Geometric Mean | 1466.3 | 933.2 | 1078 | 2126.8 |
| 95% CI | (1017.3, 2113.3) | (688.4, 1264.9) | (774.5, 1500.4) | (1586.5, 2851.0) |
| **Cmax observed (ng/mL)** | | | | |
| Geometric Mean | 146.9 | 91.5† | 139.1 | 188.2 |
| 95% CI | (96.8, 223.0) | (63.8, 131.4) | (95.3, 202.9) | (134.7, 263.0) |
| **Cmax per 0.7 mg/kg** | | | | |
| Geometric Mean | 147.9 | 92 | 128.8 | 251.7 |
| 95% CI | (99.8, 219.3) | (66.3, 127.7) | (90.2, 183.9) | (183.6, 345.1) |
| **Tmax (hr)** | | | | |
| Median ‡ | 5.53 | 6.01 | 4.46 | 5.00 |
| 95% CI § | (3.68, 7.83) | (5.01, 7.00) | (3.01, 6.04) | (4.00, 5.13) |
| **Half-Life (hr)** | | | | |
| Harmonic Mean | 4.83 | 5.59 | 5.37 | 5.72 |
| 95% CI | (4.29, 5.53) | (4.98, 6.36) | (4.77, 6.15) | (5.11, 6.50) |

† n=12. Excludes AN 4051 who received 2.5-times the intended dose.
‡ Hodges-Lehmann estimate. § Distribution-free confidence interval. CI = Confidence interval.

*B. Urinary recovery and renal clearance of losartan and E-3174*

The following tables (5 and 6) present the urine results for losartan and its metabolite in children who were toilet trained to <16 years (urine data were collected from 30 patients).

**Table 5. Summary statistics for urinary recovery and renal clearance of losartan**

| | **Group II (n=7)** | **Group III (n=9)** | **Group IV (n=14)** |
|---|---|---|---|
| **Urinary Recovery (% Dose)** | | | |
| Arithmetic Mean<br>95% CI | 2.00<br>(1.00, 3.00) | 2.80<br>(1.92, 3.68) | 2.01<br>(1.31, 2.72) |
| **Renal Clearance (mL/min/1.73m2)** | | | |
| Median †<br>95% CI ‡ | 29.54<br>(17.51, 48.59) | 56.43<br>(36.39, 118.91) | 45.30<br>(30.93, 66.57) |

† Hodges-Lehmann estimate. ‡ Distribution-free confidence interval. CI = Confidence interval.

**Table 6. Summary statistics for urinary recovery and renal clearance of E-1374**

| | Group II (n=7) | Group III (n=9) | Group IV (n=14) |
|---|---|---|---|
| **Urinary Recovery (% Dose)** | | | |
| Arithmetic Mean<br>95% CI | 2.69<br>(1.40, 3.98) | 3.58<br>(2.44, 4.72) | 3.93<br>(3.02, 4.84) |
| **Renal Clearance (mL/min/1.73m2)** | | | |
| Median<br>95% CI | 11.69<br>(6.15, 17.23) | 17.68<br>(12.80, 22.57) | 16.39<br>(12.47, 20.31) |

CI = Confidence interval.

**Assessor's Comments:**
Prior to this study, the pharmacokinetics of losartan had been studied only in adults. Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to the active carboxylic acid metabolite (E-3174); this is responsible for most of the angiotensin II receptor antagonism.

In adults, the terminal half-life of losartan and E-3174 are about 2 hours and about 6 to 9 hours, respectively. Mean peak concentrations of losartan and E-3174 are reached in 1 hour and in 3 to 4 hours, respectively. Whilst maximum plasma concentrations of losartan and E-3174 are approximately equal, the AUC of the metabolite is approximately 4 times as great as that of losartan. The pharmacokinetics of losartan and E-3174 in adults are linear with oral losartan doses up to 200 mg, and neither accumulate in plasma upon repeated once-daily dosing. Both losartan and E-3174 are highly protein bound. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in the urine as E- 3174. Biliary excretion contributes to the elimination of losartan and E-3174. Following oral $^{14}$C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the faeces. Minimal conversion of losartan to E-3174 is seen in approximately 1% of adult patients studied. Since the maturation of cytochrome P- 450 2C proteins starts during the first weeks after birth, the MAH expected that E- 3174 would be present in infants in addition to older children.

It should be noted that neither the 12.5mg tablets nor the losartan suspension that was used in this study are commercially available in the UK. The suspension was prepared for the purpose of the study with losartan 50-mg tablets, sterile water, Ora-Plus™ and Ora-Sweet SF™. Neither of these vehicles are approved for use in the UK. It is thus questionable whether the suspension, as used in the trials and presented in the FDA label can be made extemporaneously in the UK. A pharmaceutical assessment report which discusses this issue is presented separately.

This study investigated the pharmacokinetics of losartan in children with hypertension. Given the difficulties of studying children, a creditable number of patients were included, and these were also spread over appropriate age ranges. The number and timing of samples are considered adequate to characterise the pharmacokinetic profile and the dosing period was adequate to assess steady state exposure.

The pharmacokinetics of losartan and E-3174 appeared comparable in the four age groups that were examined (the pharmacokinetics of the active metabolite are of importance since it is responsible for a large proportion of the biological effect of the drug). Differences in some parameters of E-3174 were statistically significant when different age groups were compared, especially when pre-school children were compared with adolescents, but these differences are not considered to be clinically important.

With regard to a comparison between losartan pharmacokinetics in adults and children, no direct comparison from a contemporaneously undertaken clinical trial in these 2 patient groups is available. However, information on a direct comparison between children and adults is available from the FDA labelling where the table below is included, (Table 7) which shows the principal pharmacokinetic parameters in adults from historical data) and children aged ≥6 years (from Group III and IV subjects pooled together from this study). Based on these historical data, it appears that the pharmacokinetic parameters of losartan and E- 3174 in paediatric patients are generally comparable to those in adults. Mean peak concentrations of losartan and E-3174 are reached in 2 hours and in 4 hours respectively in adults and in 1 hour and 3.5 hours respectively in children. In adults, the terminal half-life of losartan and E-3174 is about 2 hours and about 6 to 9 hours, respectively. Harmonic mean half-life of losartan and E-3174 in children was about 2 and about 5 to 6 hours, respectively. When losartan is administered orally in adults, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in the urine as E-3174. Urinary recovery (% dose) of losartan and E-3174 was about 2% to 3% and about 3 to 4%, respectively, in pre-school, school-age and adolescent children (infants could not be assessed).

In conclusion, this study shows that the pharmacokinetic parameters of losartan are generally similar in infants and toddlers, pre-school children, school-age children, and adolescents. The active metabolite E-1374 is formed in children of all ages and its pharmacokinetics appear comparable in the different age groups. The study provides no information on children with severe renal impairment, as patients with GFR <30mL/min/1.73m$^2$ were excluded, nor are there data in children with hepatic impairment. In adults, data suggest significantly increased plasma concentrations of losartan in patients with hepatic impairment and this information is included as a warning in the current SmPC.

**Table 7. Pharmacokinetic parameters in hypertensive adults and children age 6-16 following multiple dosing**

| | Adults given 50mg/day for 7 days N=12 | | Age 6-16 given 0.7mg/kg/day for 7 days N=25 | |
|---|---|---|---|---|
| | Parent | Active Metabolite | Parent | Active Metabolite |
| AUC 0-24(ng•h/mL)a | 442 ± 173 | 1685 ± 452 | 368 ± 169 | 1866 ± 1076 |
| Cmax(ng/mL)a | 224 ± 82 | 212 ± 73 | 141 ± 88 | 222 ± 127 |
| T 1/2(hr) b | 2.1 ± 0.70 | 7.4 ± 2.4 | 2.3 ± 0.8 | 5.6 ± 1.2 |
| Tmax(hr) c | 0.9 | 3.5 | 2 | 4.1 |
| CLRen(mL/min)a | 56 ± 23 | 20 ± 3 | 53 ± 33 | 17 ± 8 |

a Mean ± standard deviation
b Harmonic mean and standard deviation
c Median

- **Study P216**

This was an open-label, randomized, two-period, crossover study to determine the relative bioavailability of 50-mg of a losartan suspension and losartan 50-mg tablets administered orally as single doses. It was conducted in adults, and not in children.

**Study objectives** were as follows:
(1) To assess the relative bioavailability of 50mg of a suspension and 50-mg tablet following single-dose oral administration.
(2) To compare the plasma–concentration-time profile of losartan following single-dose oral administration of 50-mg of suspension and the losartan 50-mg tablet.

(3) To compare the plasma–concentration-time profile of the metabolite L-158641 [E-3174] following single-dose oral administration of the suspension and the losartan 50-mg tablet.

**Study population**

Non-smoking healthy male and non-pregnant female subjects between 18 and 45 years of age who were within 20% of ideal body weight were recruited. A total of 16 subjects were entered as follows:-
Male (age range) 14 (21 to 42 years).
Female (age range) 2 (28 to 31 years).

**Methodology**

Each subject received each of 2 treatments which consisted of single dose oral administration of a 50-mg losartan tablet designated as Treatment A and single-dose oral administration of losartan suspension (2.5 mg/mL x 20 mL = 50 mg of losartan) designated as Treatment B in a cross-over fashion. Between each treatment period there was a washout of a minimum of 7 days.
*Pharmacokinetics*: Blood was collected over 36 hours in each treatment period following the dose of losartan for the determination of pharmacokinetic parameters for losartan and the metabolite L-158641 [E-3174]. Area under the plasma concentration-time curve ($AUC_0$- and $AUC_T$), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and apparent half-life (t½) were calculated.
*Safety*: Vital signs, laboratory safety tests, ECG measurements were obtained prestudy and poststudy. Vital signs (blood pressure and heart rate) were measured at predose, 2, 4, and 24 hours postdose in each period. Subjects were monitored for adverse events throughout the study.

**Results**

*Pharmacokinetic*: The following tables (8-11) summarise the pharmacokinetic parameters for losartan and the metabolite L-158641 [E-3174] following single-dose oral administration of the losartan 50-mg tablet and the losartan 50-mg suspension.

**Table 8.**

| | Geometric Means | | Geometric Mean Ratio† | 90% CI | 95% CI |
|---|---|---|---|---|---|
| Losartan | Suspension | Tablet | | | |
| AUC0-(ng hr/mL) | 366.3 | 395.0 | 0.927 | (0.834, 1.031) | (0.816, 1.055) |
| AUCT (ng hr/mL) | 358.4 | 387.7 | 0.924 | (0.830, 1.029) | (0.811, 1.054) |
| Cmax (ng/mL) | 208.1 | 174.2 | 1.195 | (0.984, 1.450) | (0.944, 1.512) |
| † Suspension/Tablet. | | | | | |
| From log-transformed ANOVA model. | | | | | |

**Table 9.**

| | Geometric Means | | Geometric Mean Ratio† | 90% CI | 95% CI |
|---|---|---|---|---|---|
| L-158641 (E-3174) | Suspension | Tablet | | | |
| AUC0-(ng hr/mL) | 1813.7 | 1787.1 | 1.015 | (0.912, 1.129) | (0.891, 1.156) |
| AUCT (ng | 1781.1 | 1755.8 | 1.014 | (0.910, | (0.889, |

| | | | | | |
|---|---|---|---|---|---|
| hr/mL) | | | | 1.131) | 1.158) |
| Cmax(ng/mL) | 219.0 | 211.4 | 1.038 | (0.910, 1.184) | (0.884, 1.218) |
| † Suspension/Tablet. | | | | | |
| From log-transformed ANOVA model. | | | | | |

**Table 10.**

| Tmax(hr) | | Suspension | Tablet | Difference (Suspension -Tablet) | 95% CI† |
|---|---|---|---|---|---|
| Losartan | Mean | 0.61 | 1.53 | -0.913 - | (-1.625, - |
| | Median | 0.5 | 1.13 | 0.815† | 0.250) |
| L-158641 | Mean | 3.94 | 4.56 | -0.625 - | (-2.000, |
| | Median | 4.0 | 4.5 | 1.250† | 0.500) |
| † Hodges-Lehmann Estimate of Median Difference: Exact 95% confidence interval. | | | | | |

**Table 11.**

| Half Life (t½) (Hr) | | Suspension | Tablet |
|---|---|---|---|
| Losartan | Harmonic Mean | 2.61 | 2.56 |
| | 95% CI† | (2.28, 2.93) | (2.25, 2.86) |
| L-158641 | Harmonic Mean | 6.50 | 6.36 |
| | 95% CI† | (6.12, 6.89) | (5.97, 6.75) |
| † Estimates using jackknife method. | | | |

*Safety*: There were no serious clinical, laboratory, or other adverse experiences and no subjects died during the study. No subject discontinued from the study. Only one (6%) of the 16 subjects reported a clinical adverse event. This was a non-serious blood pressure decrease rated by the investigator as mild and probably drug related after administration of the losartan 50-mg tablet (Treatment A), and malaise, pharyngitis, lymphadenopathy, and periodontitis after administration of losartan 50-mg suspension (Treatment B). There were no laboratory adverse events.

**Conclusions:**

The MAH concluded that:-

(1) The losartan 50-mg suspension and the losartan 50-mg tablet were similar in their bioavailability with respect to both losartan and L-158641 [E-3174]. Absorption of losartan following administration of the suspension is more rapid than following administration of the tablet.

(2) Single oral doses of losartan 50-mg suspension were generally well tolerated.

**Assessor's Comments**

The use of adults is considered to be an acceptable compromise which does not alter the validity of this study for children for whom it would be reasonable for the data to be extrapolated.

The sample size of 16 subjects is considered to be adequate. Blood level sampling, consisting of a blank and 30 actual samples taken over a 36 hour period, is considered to be adequate in duration and to characterise the kinetic peak.

The pharmacokinetic results of this study show that the suspension used in this study is bioequivalent to the tablet formulation in terms of AUC. However, the Cmax confidence interval (98.4 – 145%) does not meet the standard ICH criteria for equivalence. Thus the 2 formulations are not considered to be bioequivalent.

These results are only relevant to the specific suspension used in this study. A suspension formulation is not marketed in the UK. The similarities or otherwise of the formulation used in this trial to that proposed for extemporaneous manufacture in this dossier are considered in the accompanying pharmaceutical report.

**Conclusion on pharmacokinetics**

The pharmacokinetics of losartan and E-3174 appear comparable in the four age groups that were examined. Differences in some parameters were statistically significant, especially for E-3174, when the pre-school children were compared with adolescents, but these differences are not considered to be clinically important. The active metabolite E-3174 was formed from losartan in all age groups studied.

Based on historical data, it appears that the pharmacokinetic parameters of losartan and E-3174 in paediatric patients in this study are generally comparable to those in adults.

No information has been presented on children with severe renal impairment, as patients with GFR <30mL/min/1.73m$^2$ were excluded, nor are there are data in children with hepatic impairment. Data in adults suggest significantly increased plasma concentrations of losartan in patients with hepatic impairment, and a statement to this effect is included in the current SmPC.

These pk data are considered to be of value to prescribers and hence the assessor recommends that the EU SmPCs should be modified to include a summary of study P225 in Section 5.2. In addition, SmPC Section 4.2 should include a statement that use is not recommended in children with a GFR <30mL/min/1.73m$^2$ as no data exist in this group, and further that use is not recommended in children with hepatic impairment.

The 12.5mg tablet used is not currently approved in the UK. The formulation is qualitatively similar to the 25mg tablet, but differs in proportional quantities.

The 50mg tablet used has an identical core to the UK formulation with a different colourant in the film coat. This negligible difference would not be expected to effect bioavailability. Therefore, results obtained with these tablets are considered to be extrapolatable to the UK formulation. The 25mg tablet has an essentially identical core to the UK formulation but with a heavier film-coat and a different colourant. These differences would not be expected to effect bioavailability. Therefore, results obtained with these tablets are also considered extrapolatable to the UK formulation (see pharmaceutical report).

With respect to Study 216, the suspension used has not been demonstrated to be bioequivalent with the tablet formulation used.

The issues of the similarity of this suspension to that proposed for extemporaneous manufacture and the reproducibility of the extemporaneous suspension and the availability in the EU of the excipients *OraSweet* and *OraPlus* are discussed in the pharmaceutical report. The pharmaceutical assessor is of the view that the exact suspension formulation used may have a significant influence on bioavailability. Thus, results generated using this suspension cannot necessarily be applied to any other suspension using different suspending agents. There are therefore issues surrounding the pharmacokinetics of the formulations used in these studies with respect to the extrapolation of the data to the European setting.

The 12.5 mg tablet although not currently licensed in the UK and probably other EU Member States would be a useful strength for paediatric use and consequently the assessor recommends that MAH should be urged to obtain an MA for this throughout the EU as soon as practicable.

In addition a suspension formulation which is bioequivalent with tablet formulations would also be useful for paediatric use and consequently the MAH is urged to develop such a formulation for paediatric use and to obtain an MA for it in the EU as soon as practicable.

### IV.3.3 Clinical Safety and Efficacy

In respect of efficacy one clinical trial report has been submitted as follows.

-*Study 227*

This was a multicentre, double-blind, randomised dose-response study of losartan in children with hypertension.

In respect of safety, the following data have been provided:-.

Clinical Trial Data

-Pharmacokinetic study 225.
-Clinical dose ranging /efficacy study P227.

Cumulative review of safety

-Data from the extension phase of paediatric studies 225 and 227.
-Spontaneous suspected adverse reaction data.

#### IV.3.3.1 Efficacy

- **Study 227**

The efficacy of losartan was investigated in the double-blind, randomised, multicentre trial 227, which aimed at assessing the dose - response of the drug in hypertensive children.

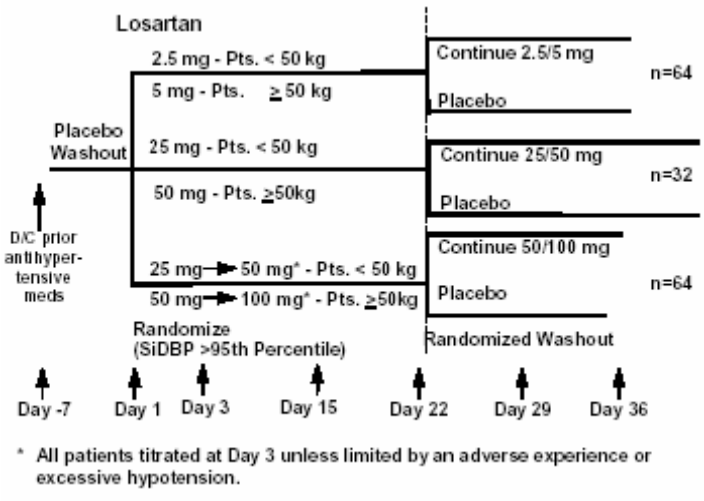
**Study objectives**

*Primary*
1) To define a dose-response relationship for losartan in hypertensive children aged 6 to 16 years after a 21-day double-blind treatment period.
2) To investigate the safety and tolerability of losartan in the dose range 2.5 to 100 mg in hypertensive children aged 6 to 16 years.

*Secondary*
To determine whether discontinuation of active losartan treatment is associated with return of hypertension.

**Study population**
The study included male and female patients aged 6-16 years with a body weight ≥20 kg and a documented history of hypertension. Patients had a mean sitting diastolic blood pressure (SiDBP) >95th percentile based on gender, height and age at the end of the 2- to 7-day washout phase. Patients had an estimated glomerular filtration rate ≥30mL/min/1.73 $m^2$ (i.e patients with severe renal impairment were excluded). Patients with severe or symptomatic hypertension, heart failure, clinically significant neurologic, respiratory, gastrointestinal, hepatobiliary, or haematological disease as well as those with a history of uncorrected coarctation of the aorta, bilateral renal artery stenosis, or renal artery stenosis to a single kidney were also excluded as were severely nephrotic patients not in remission. Previous major organ transplantation, significantly abnormal biochemical blood tests, clinically significant AV conduction disturbances and arrhythmias, pregnancy and lactation were also included among the exclusion criteria.

**Study design**
The basic study design is shown in the following figure:




The study began with a 2- to 7-day washout period in which patients discontinued their prior antihypertensive medication. Placebo suspension and placebo tablets were administered once daily during this period. If patients became hypertensive (mean trough SiDBP >95th percentile for gender, height, and age) and met all other entry criteria they qualified to enter the double-blind treatment phase. Newly diagnosed hypertensive patients had their blood pressure measured on at least 2 separate occasions before randomisation. After the washout period patients were then randomised to 1 of 3 treatment arms as follows:-
1. Low Dose; 2.5mg (patients <50 kg ) and 5 mg (patients ≥50 kg).
2. Middle Dose; 25mg (patients <50 kg ) and 50 mg (patients ≥50 kg).
3. High Dose; 50mg (patients <50 kg ) and 100 mg. (patients ≥50 kg).

Thus doses ranged from 2.5 mg to 100 mg, the maximum adult dose. In general, patients received doses ranging from 0.05 mg/kg/day to 2.5 mg/kg/day. In the 2.5/5.0mg treatment group, the study drug was administered as a suspension formulation (the same as that in the pharmacokinetic study 225). In the other treatment groups, dosing was with tablets.
Patients were assigned by allocation schedule to receive a starting dose of losartan 2.5 or 25mg (patients <50kg) and 5 or 50mg (patients ≥50kg) once daily. Patients in the high dose group who weighed <50 kg started on 25 mg and had their dose increased to 50mg unless limited by an adverse experience (at the discretion of the investigator). Similarly, patients who weighed ≥50kg started on 50 mg and had their dose increased to 100 mg.
All patients remained on the randomly assigned dose of losartan from Day 3 through to Day 22. Patients were seen as often as the investigator considered necessary, but returned to the clinic for trough blood pressure measurements at Day 15. A trough blood pressure visit was optional at Day 7.

Randomised washout: Following the 21-day double-blind treatment period, patients either underwent a randomised washout to placebo or continued active treatment for up to 14 days. Patients had blood pressure monitored at home or school and rescue medication was available. Patients returned to the clinic for trough blood pressure measurements at Day 22 and again at Day 29. The patient completed the randomised washout period at any point his/her blood pressure returned to or exceeded the baseline level. Following the randomised washout period, patients could enter an optional open label 6-month extension trial.

Blood pressure evaluation: The primary measurement for the assessment of the treatment effect on blood pressure was the change in trough SiDBP from baseline to Day 22, the end of the double-blind treatment period. A secondary measurement was the change in trough SiDBP from Day 22 to the end of the randomised washout period.

**Patient demographics and clinical characteristics**

One hundred seventy-seven (177) patients were initially randomised to the three losartan dose groups as follows:-

i. 70 patients to the low-dose group (2.5 mg: 34 patients/5 mg: 36 patients)
ii. 41 patients to the middle-dose group (25 mg: 20 patients/50 mg: 21 patients) and
iii. 66 patients to the high-dose group (50 mg: 30 patients/100 mg: 36 patients).

One hundred sixty-four patients (164) completed Period I and entered Period II as follows:-

i. 68 from the low-dose group (placebo 35 patients/losartan 33 patients)
ii. 36 from the middle-dose group (placebo 21 patients/losartan 15 patients), and
iii. 60 from the high-dose group (placebo 31 patients/losartan 29 patients)

Patient disposition is shown in Table 12.

**Table 12. Disposition of paediatric patients in study P227**

| | **Low Dose 2.5/5 mg** | **Middle Dose 25/50 mg** | **High Dose 50/100 mg** | **Total** |
|---|---|---|---|---|
| **ENTERED:** | 70 | 41 | 66 | 177 |
| Male (age range) | 38 (6 to 16) | 24 (5 to 16)† | 37 (5 to 16)† | 99 (5 to 16)† |
| Female (age range) | 32 (7 to 16) | 17 (6 to 16) | 29 (6 to 16) | 78 (6 to 16) |
| **COMPLETED:** | 68 | 36 | 60 | 164 |
| **DISCONTINUED:** | 2 | 5 | 6 | 13 |
| Clinical adverse experience | 0 | 0 | 1 | 1 |
| Laboratory adverse experience | 0 | 0 | 0 | 0 |
| Lost to follow-up | 1 | 0 | 0 | 1 |
| Deviation from protocol | 0 | 2 | 1 | 3 |
| Patient withdrew | 0 | 1 | 2 | 3 |
| Lack of efficacy‡ | 1 | 2 | 2 | 5 |

† With permission from the Merck Clinical Monitor and the investigator, 3 otherwise healthy 5-year-old children (i.e., 5 years, 10 months; 5 years, 9 months; and 5 years, 7 months) entered the study; all 3 patients were Tanner Stage >3.
‡ During or at the end of Period I. These patients had no Period II data

Patient groups were generally comparable with respect to gender, age, Tanner Stage, race, duration of hypertension (average duration 2.4 years across the treatment groups) and baseline blood pressure. The large majority of patients had at least one secondary diagnosis at the time of study enrolment. Among the most common conditions was obesity. The number of patients on prior therapy was similar across treatment groups. The most common prior antihypertensive therapies were the ACE inhibitors enalapril, lisinopril, and captopril. The most common other prior therapies were prednisone, calcium carbonate, and acetaminophen. There was also similar use of concomitant therapy across the treatment groups (54.3 to 68.2%).

**Results**

*A. Primary Hypothesis Analyses (Period I)*

The objective of the analysis for the primary hypothesis in Period I was to assess the dose response (i.e., the slope for change in trough SiDBP from Day 1 to 22) with increasing doses of losartan. Among 177 allocation numbers assigned, 2 patients each received 2 allocation numbers, and 1 patient had no post-drug blood pressure measurement. Therefore, the effective sample size in Period I was 174 patients for efficacy analyses.

In the intention-to-treat population, the mean changes were all negative (e.g., -6.01, -11.65, and -12.21 mmHg on Day 22), indicating a decrease in trough SiDBP following treatment with losartan. Increasing doses were associated with greater reductions from the low-dose to

the middle- and high-dose groups. The difference of the mean changes between the extreme doses (high versus low) was -6.2 mm Hg on Day 22 (Table 13). Comparison of middle versus high doses produced similar results.

**Table 13. Trough SiDBP (mmHg) in Period I (Day 1 to Day 22) (Intention-to-Treat population)**

| Groups | N | Day 1 | Day 22 | Mean Change (Day 22-Day 1) (SD) | 95% CI For Mean Change (Day 22-Day 1) |
|---|---|---|---|---|---|
| Low Dose | 70 | 87.92 | 81.91 | -6.01 (7.61) | -7.82, 4.19 |
| Middle Dose | 40 | 89.38 | 77.73 | -11.65 (9.08) | -14.55, -8.75 |
| High Dose | 64 | 88.8 | 76.59 | -12.21 (8.86) | -14.42, -10.00 |

When measurements were re-analysed according to patient weight (<50Kg or ≥50Kg) the results showed that again the mean SiDBP changes were all negative, indicating a antihypertensive effect in both weight groups. However, heavier patients had a numerically greater reduction in trough SiDBP than lighter patients in all dose levels. Increasing doses of losartan were associated with greater reductions for both weight groups, although in both groups the middle- and high-dose groups yielded similar results.

A stratified simple linear regression model was applied for the evaluation of change in trough SiDBP (Day 22 versus Day 1) with weight group as the stratified intercepts and dose ratio (1:10:20) as the continuous covariate. The slope analysis investigated whether increasing the dose of losartan was associated with greater reduction of the trough SiDBP. The results showed a strong dose response for losartan with a slope of -0.32 mm Hg per unit increase in dose ratio and p-value <0.0001. Patients with weight ≥50 kg had a greater mean change (2.59 mm Hg; p=0.0444) in trough SiDBP from baseline than lighter patients. The consistency of slope within each weight stratum was also investigated using the regression model with terms including weight strata, dose ratio, and interaction between weight strata and dose ratio. The test for interaction between dose ratio and weight was not significant; p=0.6327.

An ANOVA model for change in SiDBP was performed with terms including dose (low/middle/high), weight (light/heavy), and interaction between dose and weight. The mean difference between weight strata *was* significant (p=0.0379), while the interaction between dose level and weight stratum was not (p=0.8190).

Subgroup analysis explored whether the effect of losartan was consistent in prespecified patient groups. The patient characteristics and baseline variables of interest were preselected and included age, Tanner stage, gender, race and country (U.S., Non-U.S.). The results indicated a consistency in the slopes for the blood pressure response, across the categories for every subgroup variable.

*B. Secondary Hypothesis Analyses (Period II Day 22 to 36)*

The secondary objective was to determine whether discontinuation of active losartan treatment was associated with return of hypertension. The secondary hypothesis was that at the end of the subsequent 14-day, placebo-controlled washout period (Period II) following Period I, an increase in trough SiDBP between placebo-treated patients would be observed compared to losartan-treated patients. The increase for each dose level was evaluated by the difference of mean changes (placebo minus losartan) from the end of Period I (Day 22) to the end of Period II (or whenever the patient's BP returned to or exceeded baseline levels).

Among 174 patients included in the Period I analysis, 10 patients were discontinued in Period I and had no Period II blood pressure measurements. Therefore, the effective sample size in Period II was 164 patients for the efficacy analyses.

SiDBP measurements showed that for treatment groups that continued losartan therapy, the mean increases were relatively small (2.4, 2.7, and 2.6 mmHg, for low-, middle-, and high - dose groups respectively), suggesting a stable antihypertensive effect of losartan by the end of the 3-week treatment (Period I). However, there was a larger BP increase in the groups treated with placebo, in particular in the middle- and high - dose levels (3.3, 9.4, and 7.9 mmHg respectively). The difference between the treatment group means for each dose level indicated a loss of antihypertensive effect when switching to placebo (Table 14).

**Table 14. Changes in trough SiDBP (mmHg) in Period II.**

| **Groups** | | **N** | **Day 22** | **End of Period II** | **Mean Change (SD)** | **Group difference** | **95% CI** |
|---|---|---|---|---|---|---|---|
| Low | Losartan | 33 | 82.3 | 84.7 | 2.4 (9.7) | 0.9 | -3.3, 5.1 |
| | Placebo | 35 | 81.3 | 84.6 | 3.3 (7.5) | | |
| Middle | Losartan | 15 | 74.9 | 77.5 | 2.7 (8.3) | 6.7 | 0.8, 12.6 |
| | Placebo | 21 | 78.4 | 87.8 | 9.4 (9.5) | | |
| High | Losartan | 29 | 74.9 | 77.5 | 2.6 (9.0) | 5.3 | 0.1, 10.4 |
| | Placebo | 31 | 77.4 | 85.3 | 7.9 (11.2) | | |
| Mean Change = Last Measurement - measurement on Day 22. Group Difference = Placebo - losartan. | | | | | | | |

The differences between losartan and placebo were statistically significant in the middle- and high-dose groups (p=0.035 and p=0.027 respectively). Pooled data from those two groups revealed an average 6.04 mmHg difference in SiDBP between patients treated with losartan and placebo (p=0.0027).

The same set of subgroup variables as those specified for the primary efficacy analysis were used for the secondary efficacy endpoint of the mean difference of changes in trough SiDBP between low/low versus low/placebo, middle/middle versus middle/placebo, and high/high versus high-placebo treatments. Again the results showed a consistency of the mean differences across subgroups.

*C. Other parameters*

The antihypertensive effect of losartan was also estimated using sitting systolic blood pressure (SiSBP). During Period I losartan treatment showed a significant lowering effect on SiSBP, similar to that observed for the SiDBP, which was more prominent in the middle- and high-dose groups.

**Table 15. Trough SiSBP (mmHg) in Period I (Day 1 to Day 22) (Intention-to-Treat population)**

| **Groups** | **N** | **Day 1** | **Day 22** | **Mean Change (Day 22-Day 1) (SD)** | **95% CI For Mean Change (Day 22-Day 1)** |
|---|---|---|---|---|---|
| Low Dose | 70 | 129.8 | 125.4 | -4.4 (7.6) | -6.2, -2.6 |
| Middle Dose | 40 | 132.2 | 122.2 | -10.0 (9.1) | -12.9, -7.1 |
| High Dose | 64 | 128 | 119.4 | -8.6 (9.5) | -11.0, -6.3 |

Blood pressure measurements during the wash-out Period II showed an increase in SiSBP in the middle- and high-dose groups when patients discontinued losartan and switched to placebo; the differences were 5.3 and 9.3 mmHg, respectively. The difference in the low-dose group was -0.8 mmHg. The changes in SiSBP (last measurement versus Day 22) in patients

that continued on losartan were minimal, suggesting again a stable antihypertensive effect of losartan over that time period (Table 16).

**Table 16. Changes in trough SiSBP (mmHg) in Period II.**

| Groups | | N | Day 22 | End of Period II | Mean Change (SD) | Group difference | 95% CI |
|---|---|---|---|---|---|---|---|
| Low | Losartan | 33 | 125.3 | 126.8 | 1.4 (11.2) | -0.8 | -5.7, 4.2 |
| | Placebo | 35 | 124.5 | 125.2 | 0.7 (9.3) | | |
| Middle | Losartan | 15 | 118.3 | 120 | 1.7 (9.8) | 5.3 | -0.8, 11.3 |
| | Placebo | 21 | 123.2 | 130.2 | 7.0 (8.0) | | |
| High | Losartan | 29 | 120.1 | 118.9 | -1.2 (8.2) | 9.3 | 4.0, 14.7 |
| | Placebo | 31 | 118.8 | 126.9 | 8.1 (12.5) | | |
| Mean Change = Last Measurement - measurement on Day 22.<br>Group Difference = Placebo - losartan. | | | | | | | |

**Assessor's Comment**

The selected middle dose is considered equivalent to the adult starting dose (50mg) and the high dose equivalent to the maximum recommended dose in adults (100mg). In contrast, the low dose group in this study received 2.5/5mg of losartan which is 10 times lower than the middle dose. This dose is also much lower that the one used in the pharmacokinetic study 225.

The MAH's justification for the lowest dose selected is that a limited amount of information in normal adult volunteers, and in adults with heart failure, was available with losartan dosages as low as 2.5 and 5 mg from the original marketing application. The available data did not demonstrate statistically significant or clinically important blood pressure effects with these dosages in adults, although there was a suggestion of a blood pressure lowering effect in one small study with a 5 mg intravenous dose. No data with these dosages were available in paediatric or adult hypertensive patients. The MAH stated that, considering that renin levels are higher in children and, furthermore, that the renin-angiotensin system is upregulated in hypertensive patients, it was considered important to include very low dosages in the paediatric hypertension dose response study even if those dosages had not shown an effect in adults.

Accordingly, the 2.5 and 5 mg doses were selected as the lowest doses for the paediatric dose response study, as they were expected to have minimal, if any, effect on blood pressure.

The unequal number of patients in the three groups was predefined, as a result of the sample size and power calculation. The study groups were generally well balanced in terms of demographics and clinical parameters. The study was limited to patients older that 6 years but included a sufficient range of age groups up to 16 years. The proportion of school-aged children (6 to <12 years) and adolescents (12 to 16 years) was comparable between groups. This is useful as the aetiology of hypertension generally differs in different age groups. Hypertension in younger children is primarily due to renovascular or renal disease, whereas in older children essential hypertension is more common. Patients of different race were well represented, which is also useful given the accumulating evidence suggesting that there may be racial differences in the response to angiotensin receptor blockers.

An adequate number of children in each age range entered and completed the study. The definition of hypertension and the methodology of blood pressure measurement were in line with the clinical Guidelines (US National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 4$^{th}$ report 2004). The overall study design was in accordance with one of the approved designs for dose-ranging anti-hypertensive trials in children (Pasquali et al, Am Heart J 2002) which adopts a more complicated two-phase methodology to overcome technical and ethical problems such as the use of a true placebo arm. Furthermore, the choice of endpoints was adequate and the duration of the study was comparable to that of similar studies in this population and sufficient to allow the evaluation of the anti-hypertensive effect of the drug.

In light of the apparently comparable pharmacokinetics in children (especially those older than 6 years) and adults, an analogous, adjusted by weight, dosing regime would be expected to be effective. This was reflected in the selection of the middle and high dose levels. The low dose level, however, when expressed for patient body weight, gave a mean dosage of 0.07 mg/kg once daily. This is 10x lower than the starting dose for losartan in adults of 0.71 mg/kg (50 mg for a 70-kg adult). The maximum weight-adjusted mean dosage was 1.44 mg/kg once daily, which is equivalent to the maximum recommended adult dose of 1.43 mg/kg/day (100 mg for a 70-kg adult).
After three weeks of treatment (Period 1) there was a strong dose-response relationship across the dose range resulting in a slope of -0.32 mm Hg per unit
increase ($p<0.0001$) for the combined patient populations. (<50 kg and ≥50 kg). There was no evidence that the 2.5/5mg dose is effective.
The purpose of Period II was to determine whether the losartan treatment effect was lost when patients switched to placebo. The results showed an increase in blood pressure after discontinuation of losartan. The inclusion of a placebo control group strengthened the conclusion that the loss of antihypertensive efficacy was directly attributable to withdrawal of losartan therapy. Significant differences were found only in the middle and high dose groups whilst blood pressure response following discontinuation of losartan in patients who received the low dose was similar to that in patients who received placebo, providing further evidence of the lack of effect of the lowest dose employed. The additional antihypertensive effect of treatment in the highest doses compared to the middle doses was small. Some incremental effect,
however, was demonstrated and therefore some patients may benefit from doses up to 50/100mg.

Although the study was not intended to evaluate losartan effects on systolic blood pressure as the primary endpoint, this parameter was measured as well. Losartan treatment resulted in a significant dose-dependent reduction in systolic blood pressure comparable to that on the diastolic blood pressure.
All tablet strengths used in this study (25, 50 and 100mg) are commercially available. The suspension formulation is not (see pharmaceutical report).

**Conclusion on efficacy**

The results showed a significant blood pressure lowering effect of losartan in hypertensive children in doses equal or higher than 25 or 50 mg/day for patients weighing both <50 kg and ≥50 kg respectively. The lowest dose had no useful efficacy. The fact that no other doses between 2.5/5mg and 25/50mg were tested does not allow the conclusion to be drawn that the 25/50mg is the lowest effective dose. Nevertheless, the limited data provided support the contention that losartan is an effective treatment for hypertension in the paediatric population and this finding should therefore be reflected in the EU SmPCs.
The SmPC should therefore be modified to include a summary of study 227 in Section 5.1. Section 4.2 should be amended to include posology advice for the paediatric population. Statements should be included that the efficacy data are limited, and that no data exist in neonates, and in children with glomerular filtration rate <30 ml/min/1.73 $m^2$.

### IV.3.3.2 Safety Data.

#### IV.3.3.2.1 Clinical Trial Data

***Pharmacokinetic study (Study225)***

Sixteen patients reported clinical adverse events (AEs) during the study. None of the AEs were serious events and there were no deaths.

Four patients had non-serious AEs that were considered possibly related to the test drug and these included rash, headache, malaise, anorexia and irritability. None of these patients were discontinued from the study as a consequence.

Laboratory adverse events were reported for five patients. All were modest increases, compared to baseline, though not exceeding the upper normal values, in serum creatinine. One patient also had a decrease in leukocyte count that was considered possibly drug related. None of the five patients were discontinued from the study, as a consequence and all recovered.

***Clinical efficacy study (Study227)***

All adverse events (AEs) were collected during both Period I and II and serious adverse events (SAEs) were collected for a period of 14 days following the completion of the study for all 177 randomised patients, regardless of the treatment received in Period II.
In total 87 patients reported clinical AEs. The large majority were non-serious. 14 patients experienced an AE that was considered to be drug related. The most common was headache, which occurred in 2 patients (2.9%) in the low-dose group and 3 patients (4.5%) in the high-dose group.
There were no deaths during the study. Two patients on losartan had a serious adverse event during the study, both considered not related to the study drug (bronchitis requiring hospitalisation, and fracture). One patient in the high-dose group discontinued treatment due to hypotension.
Laboratory safety measurements were carried out during the study for a number of biochemical parameters. Drug related laboratory AEs were reported for five patients during the study; two of which were in the low-dose group, two in the middle-dose group, and one in the high-dose group. The laboratory values (mainly ALT and creatinine) associated with these AEs involved modest changes from baseline. None was serious and none of the patients discontinued treatment. The most common laboratory change observed, compared to baseline, was in serum potassium. There were 23 patients whose serum potassium levels increased beyond the predefined limit of change i.e. >0.5 mmol/L (the highest serum potassium value was 5.4 mmol/L). The increased serum potassium levels were slightly more prominent in the high-dose group. Only one of these changes, a serum potassium increase in the low-dose group, was considered to be “possibly” drug-related by the investigator. There were no changes in serum creatinine beyond the predefined limit of change (>26.5 µmol/L).

#### IV.3.3.2.1 Cumulative review of safety

***Paediatric clinical trials***

Safety data were submitted separately for each of the two paediatric clinical studies (see above). There was no review of these clinical trial data in the cumulative review of safety.

***Data from extension phase of paediatric studies***

After completing the acute phases of the 2 paediatric studies (225 and 227), patients were allowed to enter an optional open-label extension phase for up to 6 months. Thirty-three of 50 patients from pharmacokinetic Study 225 and 142 of 177 patients from the Losartan Dose-Response Study 227 entered the extension trial. The dose of losartan and the number of visits during this period were left to the discretion of the investigator. Adverse events were monitored throughout this period in all patients. Laboratory safety measurements including haematology, blood chemistry and urinalysis were also performed at the end of the 6-month extension phase, at the time of discontinuation, or whenever was clinically indicated.

In total, adverse events were reported in 90 patients. A summary is presented in Table 13.

**Table 13. Summary of clinical adverse events during the extension phase of Losartan paediatric studies**

| **Clinical Adverse Events (AEs)** | N=175 | |
|---|---|---|
| | n | (%) |
| With one or more AEs | 90 | (51.4) |
| With no AE | 85 | (48.6) |
| With drug-related* AEs | 6 | (3.4) |
| With serious AEs | 12 | (6.9) |
| With serious drug-related* AEs | 0 | (0.0) |
| Deaths | 0 | (0.0) |
| Discontinued therapy due to an AE | 3 | (1.7) |
| Discontinued therapy due to a drug-related* AE | 1 | (0.6) |
| Discontinued therapy due to a serious AE | 2 | (1.1) |
| Discontinued therapy due to a serious drug-related* AE | 0 | (0.0) |
| *Determined by the investigator to be possibly, probably, or definitely drug related | | |

A total of 6 patients had clinical AEs that were determined by the investigators to be possibly or probably drug related. Back pain was the most common; reported in 2 out of the 6 patients. Only one patient discontinued during the extension phase due to a clinical adverse experience (asthenia/fatigue) that was considered possibly related to losartan therapy. Serious adverse events were reported for 12 patients but all were considered as non drug-related. There were no deaths.

A total of 12 patients had a drug-related laboratory adverse events. Four patients had increased ALT and upon completion of the study, 3 of these patients had ALT values above the normal range (62, 68 and 107 iu/L respectively). Two patients had increased serum creatinine (up to 114.9 and 132.6 µmol/L respectively) that caused both patients to discontinue from the study. No follow-up information has been provided on these cases.

***Assessor's Comments***

The safety data from the two paediatric studies, and during the extension phase revealed no serious drug-related clinical adverse events and no deaths. A number of non serious AEs and laboratory abnormalities were recorded but were of the expected type and within the expected range respectively, given the pharmacology of the drug and its known safety profile in the adult population. Given the small number of patients and the short duration of the trials, the overall incidence of AEs does appear relatively high. However, the study populations included patients with serious concomitant diseases, which might explain to some extent the occurrence of a number of AEs that were not related to study treatment.

***Spontaneous data to 30 April 2004***

The Merck Worldwide Adverse Experience System (WAES) database was searched to identify reports that had been received by the company and entered into the database from market introduction until 30 April 2004 and which refer to patients less than 18 years of age who had been exposed to, or treated with, losartan and where losartan was the primary suspect therapy of an adverse event(s) described in the report.

This search revealed 55 reports. The reports included 35 spontaneous cases submitted to the company from the marketplace. Two reports were from the medical literature. Twenty reports from the acute and extension phase of the clinical trials (225 and 227) were also identified. The cases have been tabulated into age groups (see Table 14).

**Table 14. Number of reports in the different age groups**

| | Birth to 1 month | 1 month to 2 years | >2 to 12 years | >12 to <18 years |
|---|---|---|---|---|
| Spontaneous Reports | 1 | 11 | 19 | 4 |
| Serious Clinical Trial Reports | 0 | 4 | 8 | 8 |

For the first age group, there was only 1 spontaneous report regarding a 4-week-old male with a rash who was breast-fed while his mother was being treated with losartan for hypertension. The mother also received amlodipine and atorvastatin. Losartan was discontinued on an unknown date. Amlodipine and atorvastatin were also stopped and the rash slowly improved.

In the older children there were in total 14 reports that involved overdose (accidental ingestion and one case of suicide attempt) of losartan at doses between 25 and 1500mg. Only in 4 of these cases was an adverse event was reported in association with the overdose. One report describes a 2-year-old female who died of acute respiratory arrest followed by asystole having accidentally ingested several medications including losartan at an unknown dose. In two other cases, patients developed hypotension and sinus tachycardia after ingesting losartan at doses of 350mg and 50mg respectively. In one report an 11-year-old female attempted to commit suicide with losartan along with acebutolol, thyroxin, fluoxetine, paracetamol, atenolol and prednisolone. She was hospitalised, underwent gastric lavage and recovered.

In the remaining 20 spontaneous reports in the age groups older that one-month, patients were treated with losartan for various indications most commonly hypertension, heart failure and renal disorders. In many of these reports, adverse events were considered not to be related to losartan treatment, whilst in others there was very limited information on the clinical conditions, posology and the event itself that could allow a proper assessment of causality. Reported adverse events included exanthema, urticaria, fatigue, cough and hypotension. There was one report for a 6-year-old female who developed "hepatic failure" (though no laboratory values are available) 2 months after starting losartan 12.5mg daily for hypertension. Losartan was discontinued and the "hepatic failure" persisted, according to the report. No information on concomitant illnesses, other medication or follow-up was provided on that case.
There were 7 reports of acute renal failure. In all of them there were significant underlying confounding disorders including congenital heart disease, heart failure and impaired renal function, and multiple concomitant medications, such that causality cannot be attributed to losartan in these cases.

**Assessors Comments**
The data from the company's database appear to be of limited help in further evaluating the safety of losartan in children. The small number of reports, together with the lack of detailed information and the presence of multiple confounding factors in many cases do not allow firm conclusions to be drawn. As with the clinical trial data, in many cases patients suffered from diseases which have probably contributed to the adverse events described. However, there are no clear signals for any drug-related unexpected reactions.

***Safety Addendum for period 01 May 2004- 30 April 2006.***

In the dossier the MAH has provided an update for reported adverse events to the Company occurring in children for the period 01/05/2004 – 30/04/2006. During this period no serious reports were received by the MAH in relation to clinical trials in children, and 3 serious

reports were received in relation to suspected adverse reactions form the market place. These were as follows:

Case 1 (WAES 0509GBR00005) was of a "prescribed" overdose of losartan in a 4-year-old child with Henoch-Schonlein Purpura. The dose and duration of use is not known. The report states that the patient did not experience any adverse effects.

Case 2 (WAES 0508USA01136) describes a 14-year-old male with multiple pathologies (Burkitt's lymphoma (1993), neurogenic bladder (November 1998), renal dysplasia (November 1998), vesicoureteric reflux (November 1998), urinary tract infection (April 2003), who was prescribed losartan 25 mg daily for treatment of nephropathy.
Concomitant therapy included alfacalcidol, sulfametholxazole + trimethoprim and cephalexin. Approximately 2 weeks after receiving losartan he suffered acute renal failure which recovered following haemodialysis.

Case 3 (WAES 0602ISR00005) was a 16-year-old male with Type I diabetes who received losartan at an unknown dose for an unknown duration for the treatment of proteinuria. Subsequently, the patient developed angioedema, which was successfully treated with antihistamines and corticosteroids.

The MA Holder points out that angioedema and renal failure are "listed" adverse events for losartan, and that these data do not suggest that the safety profile of losartan is different for paediatric patients (<18 years of age) than for adults.

**Assessors Comments**
These data add nothing further to the known safety profile of losartan in children. As stated by the MAH, the renal failure and angioedema are adverse effects already listed in the SmPC for *Cozaar*.

**Conclusion on safety**
Overall, the data suggest that losartan is well tolerated in children. Reported events were often related to renal impairment or liver function abnormalities which are currently "labelled" for Cozaar. Although the amount of information both in terms of the number of patients exposed to the drug and the length of exposure are limited, the information provided raise no significant concerns of any increased risk for children compared to adults. There is no information on the drug effects in potentially vulnerable patient groups such as those with severe renal or hepatic impairment; therefore the SmPC should state that the drug should not be used in children with these conditions. There are no long term safety data in children to provide reassurance that losartan has no effect on growth or puberty, and no long term efficacy data to provide reassurance that the drug has a beneficial effect in reducing cardiovascular morbidity and mortality. The SmPC should be amended to state this.

The following statements should therefore be included into the SmPC:-

**Section 4.2 Posology and method of administration**
Use in children and adolescents:
-Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available.
-Losartan is not recommended in children with hepatic impairment.

**4.8 Undesirable effects**
Data in children are limited. However, the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

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

### IV.3.3.3 Other data

**Publications**

*-Ref 1.* *Sh. Shahinfar et al A Double-Blind, Dose–Response Study of Losartan in Hypertensive Children,. AJH 2005; 18:183–190.*

**Assessor's Comment**
This publication describes study 227, and adds nothing further to the previous discussion of this trial.

*-Ref 2.* *D.Ellis et al. Antihypertensive and Renoprotective Efficacy and Safety of Losartan; AJH 2004; 17:928–935.*

This paper describes an open-label non comparative long term study where losartan was administered to 45 consecutive children presenting with either hypertension alone (H) n=28, or hypertension plus proteinuria (H + P) n=34.

Recruited patients were suffering from a variety of renal parenchymal disorders; the commonest were IgA/Henoch-Schonlein purpura (10 cases) membrano-proliferative glomenulonephritis (5 cases) and reflux nephropathy (8 cases). The mean age of recruited patients was 12.9 years (range 3.7-17.9) mean GFR was 99.4mL/min/1.73m$^2$ (SD ± 6.4). The mean protein excretion in those with proteinuria was 3126 ± 548mg/day (2481 ± 529mg/m$^2$/day). Losartan was commenced at a dose approximating 0.8mg/kg/day as a single dose. Increments were made weekly if BP was >90$^{th}$ centile or in the H + P group if proteinuria did not fall below 50% of baseline excretion. Assessments were made at 4 visits at <0.25 years, ≥0.25, <0.5 years, 0.5-1.0 year and > 1 year. BP, GFR and proteinuria were the outcome measures.
At the end of the study the mean dose was 1.0mg/kg/day (±0.1mg/kg/day). Compared with baseline systolic, diastolic and mean BP (MABP) fell by 9-12mmHg. These were significant changes ($p < 0.01$). In the H + P group reduction in proteinuria of 66-71% was observed in visits II to IV ($p < 0.01$). GFR declined at a rate of 1.4mL/min/1.73m$^2$/year. Adverse events led to 5 discontinuations during the study. One event was serious – a case of hyperkalaemia in a patient also treated with ACE inhibitors.
The authors conclude that losartan was associated with sustained antihypertensive and seroprotective benefits in children with a variety of chronic renal parenchymal disorders, and was generally well tolerated.

**Assessor's Comments**
The effect of losartan on adults with proteinuria is well known. These data provide reassurance that similar efficacy exists in children. In this regard the current SmPC (UK) states in Section 5.1:
"…in non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction."
This text accurately describes the findings in the Study Ref 2. Consequently no further SmPC modification is considered necessary as a consequence of these data.

# V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Losartan is an angiotensin-II receptor (type AT1) antagonist. The data provided to support paediatric exclusivity in the US have previously been considered in the UK as a national procedure and the UK SmPC amended following a subsequent national variation procedure on 14th November 2005. This clinical assessment for the EU Worksharing procedure is essentially that previously performed by the UK for the national procedure in 2004, but those new data which have been presented for the first time in this dossier (i.e. the Addendum 01 May 2004 – 30 April 2006 and the new publications) have been assessed in addition.
The Clinical Expert Overview is by Merck and Co Inc, Rahway, New Jersey, USA. The proposal in this document (that as data are limited to those aged more than 1 month and that no patients with hepatic impairment were included that no dosing recommendations will be included for these groups) appears reasonable and is endorsed.

The MAH has submitted the results from two studies in children investigating the effect of losartan on pharmacokinetic parameters and on blood pressure in hypertensive children. The use of children in antihypertensive trials is problematic due to a relatively low incidence and prevalence, the lability of blood pressure values, and technical problems in measurement of blood pressure. In this context, both studies included a sufficient number of patients and were well designed and conducted.

The pharmacokinetics of losartan and E-3174 appear comparable in the four age groups that were examined. Differences in some parameters were statistically significant, especially for E-3174, when pre-school children were compared with adolescents, but the differences are not considered to be clinically important. The active metabolite E-3174 was formed from losartan in all age groups studied.
Based on historical data, it appears that the pharmacokinetic parameters of losartan and E-3174 in paediatric patients in this study are generally comparable to those in adults. No information has been presented on children with severe renal impairment, as patients with GFR <30mL/min/1.73m$^2$ were excluded, nor are there are data in children with hepatic impairment.
These pk data are considered to be of value to prescribers and hence the EU SmPCs should be modified to include a summary of study 225 in Section 5.2. In addition SmPC Section 4.2 should include a statement that use is not recommended in children with a GFR <30mL/min/1.73m$^2$ as no data exist in this group, and that use is not recommended in children with hepatic impairment.

With respect to Study 216, the suspension used has not been demonstrated to be bioequivalent with the tablet formulation used. The issues of the similarity of this suspension to that proposed for extemporaneous manufacture and the reproducibility of the extemporaneous suspension and the availability in the EU of the excipients *OraSweet* and *OraPlus* are discussed in the pharmaceutical report, and there are concerns in this area. The exact suspension formulation used may have a significant influence on bioavailability. Thus, results generated using this suspension cannot necessarily be applied to any other suspension using different suspending agents. There are therefore issues surrounding the pharmacokinetics of the formulations used in these studies with respect to the extrapolation of the data to the European setting.

The 12.5 mg tablet is not currently licensed in the UK and probably other EU Member States in addition. It would be a useful strength for paediatric use and consequently the MAH is urged to obtain an MA for this throughout the EU as soon as practicable.

In addition, a suspension formulation which is bioequivalent with tablet formulations would be useful for paediatric use and consequently the MAH is urged to develop such a formulation for paediatric use and to obtain an MA for it in the EU as soon as practicable.

With regard to efficacy the results of study 227 showed a significant blood pressure lowering effect of losartan in hypertensive children in doses equal or higher than 25 or 50 mg/day for patients weighing both <50 kg and ≥50 kg respectively. The lowest dose (2.5/5mg) had no useful efficacy. The fact that no other doses between 2.5/5mg and 25/50mg were tested does not allow the conclusion to be drawn that the 25/50mg is the lowest effective dose. Nevertheless, the limited data provided support the contention that losartan is an effective treatment for hypertension in the paediatric population and this finding should therefore be reflected in the EU SmPCs.
The SmPC should therefore be modified to include a summary of study 227 in Section 5.1. Section 4.2 should be amended in addition to include posology advice for the paediatric population. Statements should be included in this Section that the efficacy data are limited, and that as no data exist in those aged <1 month of age, and in children with glomerular filtration rate <30 ml/min/1.73 $m^2$, use cannot be recommended in these individuals. .
These data are considered to be of value to prescribers and hence the EU SmPCs should be modified to include a summary of study 227 in Section 5.1.

In respect of safety, data are limited both in terms of the number of patients exposed to the drug and the length of exposure, but suggest that losartan is well tolerated in children. Reported events were often related to renal impairment or liver function abnormalities which are currently "labelled" for *Cozaar*. The information provided raises no significant concerns of any increased risk for children compared to adults. There is no information on the drug effects in potentially vulnerable patient groups such as those with severe renal or hepatic impairment; therefore, as stated above, the SmPC should state that the drug should not be used in children with these conditions. There are no long term safety data in children to provide reassurance that losartan has no effect on growth or puberty, and no long term efficacy data to provide reassurance that the drug has a beneficial effect in reducing cardiovascular morbidity and mortality. The SmPC should be amended to state this.

In the light of the available data the following safety statements should be included into the SmPC as an aid to prescribers:-

**Section 4.2 Posology and method of administration**
Use in children and adolescents:
-Losartan is not recommended in neonates and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available.
-Losartan is not recommended in children with hepatic impairment.

**4.8 Undesirable effects**
Data in children are limited. However, the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

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

No SmPC change is recommended as a consequence of consideration of the new publications.

# VI. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEUR

None

# VII. CONDITIONS FOR THE APPROVAL AS PROPOSED BY THE RAPPORTEUR

1. The Co-Rapporteur recommends that as significant supportive data and experience now exists in the paediatric population that the SmPC for *Cozaar* should be modified to summarise these data.
In particular:-

1.1 Section 4.2 (posology and method of administration) should be modified to include dosing advice for children and adolescents, as follows:-

*For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients 20 to <50 kg, and 50 mg once daily in patients ≥50 kg. The dosage should be individually adjusted to a maximum of 50 mg daily in patients weighing 20 to <50 kg, and 100 mg in patients ≥50 kg.*

Together with the following caveats:-

1.1.1 A statement should be included that there are limited data on efficacy, safety and pharmacokinetics in hypertensive children and adolescents.
1.1.2 A statement should be included that losartan is not recommended for use in neonates aged < 1 month of age as no data exist in these patients.
1.1.3. A statement should be included that losartan is not recommended for use in neonates and in children with glomerular filtration rate <30 ml/min/1.73 $m^2$, as no data are available in these patient groups.
1.1.4. A statement should be included that lLosartan is not recommended in children with hepatic impairment.

1.2 Section 4.8 (Undesirable effects).
A statement should be included that data in children are limited. However, the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

1.3 Section 5.1 (Pharmacological Properties).

1.3.1 A summary of study 227 should be included in this Section.
1.3.2 A statement should be included that the long-term effects of losartan on growth, puberty and general development have not been studied.
1.3.3 A statement should be included that the long-term efficacy of losartan therapy in childhood to reduce cardiovascular morbidity and mortality has not been established.

1.4 Section 5.2 (Pharmacokinetic Properties).

A summary of study 225 should be included in this Section.

2. The Patient Information Leaflet should be modified in line with the proposed SmPC changes.

3. The assessment report should be published on the HOA webpage.

4. As the 12.5 mg tablet is considered to be a useful strength for paediatric use, the MAH is encouraged is to obtain an MA for this product throughout the EU as soon as practicable.

5. A suspension formulation which is bioequivalent with tablet formulations is considered to be a useful product for paediatric use. Therefore the MAH is encouraged is to obtain an MA for such a product throughout the EU as soon as practicable.

# ANNEX I:

# PROPOSED CHANGES TO THE SPC, ANNOTATED WITH THE RAPPORTEUR'S COMMENTS AFTER EACH SECTION

## 1. NAME OF THE MEDICINAL PRODUCT

<<COZAAR® 100 mg Film Coated Tablets>>
<<COZAAR® 50 mg Film Coated Tablets>>
<<COZAAR® 25 mg Film Coated Tablets>>

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

There are three strengths of 'Cozaar' Tablets available:

<<Each 'Cozaar' 100 mg Tablet contains 91.6 mg of losartan, present as 100 mg of losartan potassium.>>
<<Each 'Cozaar' 50 mg Tablet contains 45.8 mg of losartan, present as 50 mg of losartan potassium.>>
<<Each 'Cozaar' 25 mg Tablet contains 22.9 mg of losartan, present as 25 mg of losartan potassium.>>
For excipients see section 6.1

## 3. PHARMACEUTICAL FORM

Film-coated tablet
<<'Cozaar' 100 mg Tablet is supplied as a white, teardrop-shaped, film-coated tablet marked '960' on one side and plain on the other.>>
<<'Cozaar' 50 mg Tablet is supplied as a white, oval-shaped, film-coated tablet marked '952' on one side and a single score line on the other.>>
<<'Cozaar' 25 mg Tablet is supplied as a white, oval-shaped, film-coated tablet marked '951' on one side and plain on the other.>>

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Hypertension*
'Cozaar' is indicated for the treatment of hypertension.

*Hypertensive patients with left ventricular hypertrophy*
In hypertensive patients with left ventricular hypertrophy a reduced risk of stroke was demonstrated. The data do not support the use of 'Cozaar' for this indication in black patients (see section 4.4 'Special warnings and Precautions for Use-*Race'* and section 5.1 Pharmacodynamic Properties, LIFE study, *Race*).

*Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria)*
'Cozaar' is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

## 4.2 Posology and method of administration

'Cozaar' may be administered with or without food.
'Cozaar' may be administered with other antihypertensive agents. The concomitant use of 'Cozaar' and ACE inhibitors has not been adequately studied.

*Hypertension*
The starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily.

*Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy*
The usual starting dose is 50 mg of 'Cozaar' once daily. A low dose of hydrochlorothiazide may be added and/or the dose of 'Cozaar' may be increased to 100 mg once daily based on blood pressure.

*Renal protection in type 2 diabetic patients with nephropathy.*
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily according to blood pressure response from one month after initiation of therapy onwards. 'Cozaar' may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

'Cozaar' was not studied in type 2 diabetic patients with severe renal impairment.

*Use in patients with intravascular volume depletion*: For the very small proportion of patients who have intravascular volume depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily is recommended (see 4.4 'Special warnings and precautions for use').

*Use in renal impairment*: No initial dosage adjustment is necessary in patients with mild renal impairment (i.e. creatinine clearance 20-50 ml/min). For patients with moderate to severe renal impairment (i.e. creatinine clearance <20 ml/min) or patients on dialysis, a lower starting dose of 25 mg once daily is recommended.

*Use in hepatic impairment*: A lower dose should be considered for patients with a history of hepatic impairment (see 4.4 'Special warnings and precautions for use').

*Use in the elderly*: *Patients up to 75 years*: No initial dosage adjustment is necessary for this group of patients.

*Patients over 75 years*: Presently there is limited clinical experience in this group; a lower starting dose of 25 mg once daily is recommended.

*Use in children and adolescents:* There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 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. 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 starting dose is 50 mg once daily. 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 pediatric patients.

Losartan is not recommended in neonates aged < 1 month and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available in ~~this~~ these patient groups.

Losartan is also not recommended in children with hepatic impairment.

**Assessor's Comments**
-The proposals in respect of the extemporaneous suspension formulation are not supported and hence reference to this formulation should be deleted from the SmPC. Poslogy advice therefore needs amending in line with the lack of the suspension formulation.
-Minor modifications are proposed to the MAH text to improve clarity as follows:-
*Losartan is not recommended for use in neonates aged < 1 month and in children with glomerular filtration rate < 30 ml/min/1.73 $m^2$, as no data are available in these patient groups.*

### 4.3 Contraindications

'Cozaar' is contraindicated in pregnancy (see 4.6 'Pregnancy and lactation') and in patients who are hypersensitive to any component of this product.

### 4.4 Special warnings and precautions for use

*Hypersensitivity*:
Angioedema. See 4.8 'Undesirable effects'.

The use of 'Cozaar' in patients with haemodynamically significant obstructive valvular disease or cardiomyopathy has not been adequately studied.

*Hypotension and electrolyte/fluid imbalance*
In patients who are intravascularly volume depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of 'Cozaar', or a lower starting dose should be used (see 4.2 'Posology and method of administration').

In paediatric patients who are intravascularly volume-depleted, the~~se~~ condition~~s~~ should be corrected prior to administration of 'Cozaar'.

**Assessor's Comments**
-The MAH's proposal is endorsed. The plurality should be deleted.

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with 'Cozaar' as compared to the placebo group (see 4.8 'Undesirable effects' and *Laboratory test findings*).

*Liver function impairment*
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see 4.2 'Posology and method of administration' and 5.2 'Pharmacokinetic properties').

*Renal function impairment*

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy.

Caution is required in patients with significant renal disease and renal transplant recipients as there have been reports of anaemia developing in such patients treated with 'Cozaar'.

*Race (Black patients)*
There is no evidence that Cozaar reduces the risk of stroke in black patients with hypertension and left ventricular hypertrophy (see Section 5.1 Pharmacodynamic properties, LIFE Study, *Race'*).

## 4.5 Interaction with other medicinal products and other forms of interaction

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, ketoconazole, erythromycin and phenobarbital (phenobarbitone). Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium or may increase potassium levels (e.g. potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium) may lead to increases in serum potassium. Co-medication is not advisable.

As with other antihypertensive agents, the antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs such as indomethacin.

## 4.6 Pregnancy and lactation

*Use during pregnancy*
Although there is no experience with the use of 'Cozaar' in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.

In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester; thus, risk to the foetus increases if 'Cozaar' is administered during the second or third trimesters of pregnancy.

**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and even death in the developing foetus. 'Cozaar' should not be used in pregnancy, and if pregnancy is detected 'Cozaar' should be discontinued as soon as possible.**

*Use during lactation*
It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to

discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

### 4.7 Effects on ability to drive and use machines

There are no data to suggest that 'Cozaar' affects the ability to drive and use machines.

### 4.8 Undesirable effects

Side effects have usually been mild and transient in nature and have not required discontinuation of therapy. The overall incidence of side effects reported with 'Cozaar' was comparable to placebo.

In controlled clinical trials for essential hypertension, dizziness was the only side effect reported as drug related that occurred with an incidence greater than placebo in 1% or more of patients treated with 'Cozaar'. In addition, dose-related orthostatic effects were seen in less than 1% of patients.

Data are limited in the paediatric population. However the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

**Assessor's Comments**
-The MAH's proposal is generally endorsed. However to improve clarity modification is proposed to the MAH text as follows:-
*Data are limited in the paediatric population. However the adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.*

'Cozaar' was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue and vertigo.

'Cozaar' was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with nephropathy. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalaemia. In this study, few patients discontinued due to hyperkalaemia (see 4.4 'Special warnings and precautions for use, *Hypotension and electrolyte/fluid imbalance'*).

The following adverse reactions have been reported in post-marketing experience:

*Hypersensitivity*: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schonlein purpura, has been reported rarely.

*Gastro-intestinal*: Hepatitis (reported rarely), diarrhoea, liver function abnormalities.

*Haematologic*: Anaemia (see 4.4 'Special warnings and precautions for use'), thrombocytopenia (reported rarely).

*Musculoskeletal*: Myalgia, arthralgia.

*Nervous system/Psychiatric*: Migraine.

*Respiratory*: Cough.

*Skin*: Urticaria, pruritus, rash.

*Laboratory test findings*
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of 'Cozaar'. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with 'Cozaar' and 3.4% of patients treated with placebo developed hyperkalaemia (see 4.4 'Special warnings and precautions for use, *Hypotension and electrolyte/fluid imbalance'*). Serum potassium should be monitored, particularly in the elderly and patients with renal impairment. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

## 4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1,000 mg/kg (3,000 mg/m$^2$) and 2,000 mg/kg (11,800 mg/m$^2$) (500 and 1,000 times the maximum recommended daily human dose*), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

*Based on a patient weight of 50 kg.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

ATC code: CO9C A
Losartan is an oral, specific angiotensin-II receptor (type $AT_1$) antagonist. Angiotensin II binds to the $AT_1$ 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 proliferation. Based on binding and pharmacological bioassays, it binds selectively to the $AT_1$ receptor. *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.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the $AT_1$ receptor and does not bind to or 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, effects not directly related to blocking the $AT_1$ receptor, such as the potentiation of bradykinin-mediated

effects, the generation of oedema (losartan 1.7%, placebo 1.9%) or fatigue (losartan 3.8%, placebo 3.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

A study was carried out which was specifically designed to assess the incidence of cough in patients treated with 'Cozaar' as compared to patients treated with ACE inhibitors. In this study and in the controlled clinical trials for hypertension, the incidence of cough reported by patients receiving 'Cozaar' or an agent not associated with ACE-inhibitor-induced cough (hydrochlorothiazide or placebo) was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4,131 patients, the incidence of spontaneously reported cough in patients treated with 'Cozaar' was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally, losartan causes a decrease in serum uric acid (usually <24 micromol) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium administered in doses of up to 150 mg once daily did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

*Hypertension Studies*
In clinical studies, once-daily administration of 50 mg 'Cozaar' to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of 'Cozaar' had no clinically significant effect on heart rate.

The antihypertensive effect of 50 mg of 'Cozaar' is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of 50-100 mg of 'Cozaar' is comparable to once-daily administration of atenolol 50-100 mg. The effect of administration of 50-100 mg of 'Cozaar' once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (≥65 years) after 12 weeks of therapy.

Although 'Cozaar' is antihypertensive in all races, as with other drugs that affect the renin-angiotensin-aldosterone system, black hypertensive patients have a smaller average response to losartan monotherapy than non-black patients.

If ‘Cozaar’ is given together with thiazide-type diuretics, the blood-pressure-lowering effects are approximately additive.

LIFE Study
The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily Cozaar’ 50 mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of ‘Cozaar’ or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure. The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with ‘Cozaar’ resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with ‘Cozaar’ reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

*Race:* There were 533 black patients in the study. In this group, treatment with ‘Cozaar’ resulted in a 67% increase in risk compared with atenolol for the primary composite endpoint (p=0.033, 95% confidence interval 1.04-2.66) and a 118% increase relative to atenolol in the risk of stroke (p=0.030, 95% confidence interval 1.08-4.40).

RENAAL Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a multicentre, randomised, placebo-controlled, double-blind study 1,513 type 2 diabetic patients with nephropathy (751 treated with ‘Cozaar’), with or without hypertension. Patients were recruited with proteinuria as defined by urinary albumin to creatinine ratio >25 mg/mmol or 24-hour urinary protein excretion >500 mg and a serum creatinine of 115-265 micromol/l (a lower limit of 133 micromol/l was used for patients weighing more than 60 kg). The patients were randomised to receive ‘Cozaar’ 50 mg once daily, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg daily as appropriate after one month; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for 3.4 years on average.

The results showed that treatment with ‘Cozaar’ (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p=0.022) in the number of patients reaching the primary composite endpoint, of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The benefit exceeded that attributable to changes in blood pressure alone. For the following individual and combined components of the primary composite end point, the results also showed significant risk reduction in the group treated with ‘Cozaar’: 25.3% risk reduction in doubling of serum creatinine (p=0.006); 28.6% risk reduction in end-stage renal disease (p=0.002); 19.9% risk reduction in end-stage renal disease or death (p=0.009); 21.0% risk reduction in doubling of serum creatinine or end-stage renal disease (p=0.010). All-cause mortality alone was not significantly different between the two treatment groups.

For the secondary endpoints, the results showed an average reduction of 34.3% in the level of proteinuria in the group treated with 'Cozaar' ($p<0.001$) over the mean of 3.4 years. Treatment with 'Cozaar' reduced the rate of decline in renal function during the chronic phase of the study by 13.9%, $p=0.003$ (median rate of decline of 25.5%, $p<0.0001$) as measured by the reciprocal of the serum creatinine concentration-time curve. There was no significant difference between the group treated with 'Cozaar' (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality, although the study was not powered to detect such an effect.

*Paediatric Hypertension*

The antihypertensive effect of 'Cozaar' was studied in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73m$^2$. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 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, the two higher doses reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used by each group. The dose response to losartan was observed across all subgroups (e.g. age, Tanner stage, gender, race). However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not have useful antihypertensive efficacy. When patients were randomised to continue either losartan or placebo, after three weeks of therapy, trough diastolic blood pressure rose in patients receiving placebo between 5 and 7 mmHg more than patients receiving losartan at the two higher doses. However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those who continued losartan at the lowest dose in each group, again suggesting that the lowest dose in each weight group (2.5 mg and 5 mg) 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.

**Assessor's Comments**

-The MAH's proposal is generally endorsed. However to improve clarity the following changes are proposed.

Para 1. *The antihypertensive effect of 'Cozaar' was studied in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73m$^2$.*

*However, the lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/kg, did not have useful antihypertensive efficacy.*

*However, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those who continued losartan at the lowest dose in each group, again suggesting that the lowest dose in each weight group (2.5 mg and 5 mg) did not have significant antihypertensive effect.*

## 5.2 Pharmacokinetic properties

*Absorption*

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

*Distribution*
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

*Biotransformation*
About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of $^{14}$C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

*Elimination*
Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of $^{14}$C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

*Characteristics in patients*
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

*Pharmacokinetics in paediatric patients*
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The results showed that the active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite were generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

**Assessor's Comments**
-The MAH's proposals are endorsed.

## 5.3 Preclinical safety data

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174).

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

‘Cozaar’ Tablets contain the following excipients:

hydroxypropyl cellulose E463
hypromellose E464
lactose monohydrate
magnesium stearate E572
microcrystalline cellulose E460
pregelatinised starch
titanium dioxide E171
carnauba wax.

‘Cozaar’ 100 mg also contains 8.48 mg (0.216 mmol) of potassium.
‘Cozaar’ 50 mg also contains 4.24 mg (0.108 mmol) of potassium.
‘Cozaar’ 25 mg also contains 2.12 mg (0.054 mmol) of potassium.

## 6.2 Incompatibilities

None.

## 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

### 6.5 Nature and contents of container

White, opaque PVC/PE/PVDC blisters with aluminium foil lidding in packs of 7 and 28 tablets.

### 6.6 Instructions for use/handling

None.

## 7. MARKETING AUTHORISATION HOLDER

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

July 2007.

**LEGAL CATEGORY:**

POM

# ANNEX

# Pharmaceutical assessment report

## Losartan Potassium (Cozaar): Pharmaceutical aspects

- **Summary**

The US and EU tablet formulations are sufficiently similar that clinical data obtained using the US tablet may reasonably be applied to the EU formulation.

The OraSweet/OraPlus suspension is manufactured using acceptable ingredients. This suspension is adequately specified except for the need for an additional limit for unknown degradation products. The efficacy of the preservative system should be confirmed at the lower limits of the specification. The stability of the suspension is proven.

The suspension is pharmaceutically acceptable with the minor provisos listed above, but there is a significant issue about the bioequivalence of the suspension when compared to the tablet formulation. This suspension is bioequivalent to the tablet formulation in terms of total availability (AUC), but the Cmax confidence interval (98.4 – 145%) does not meet the standard ICH criteria for equivalence.

- **Pharmaceutical aspects**

**Formulations used in clinical studies**
The formulations used in the pivotal clinical studies were US tablet formulations containing 12.5mg, 25mg or 50mg of losartan and an unlicensed suspension.

**Tablet formulations**
The 50mg tablet used in thre clinical studies was an identical core to the EU formulation. The US film-coat was equal in weight but contained a different colourant. This negligible difference would not be expected to effect bioavailability. Therefore, results obtained with these tablets can also be projected to the EU formulation.

The 25mg tablet was an essentially identical core to the EU formulation. The US film-coat was heavier than the EU coat and contained a different colourant. These differences are minor and would not be expected to effect bioavailability. Therefore, results obtained with these tablets can also be projected to the EU formulation.

The 12.5mg tablet is not approved in the EU. The formulation is qualitatively similar to the 25mg tablet, but does differ in proportional quantities.

**Suspension formulation**
The unlicensed suspension used in the clinical studies was manufactured using a US formulation 50mg tablet. This is an identical core to the EU formulation. The suspension was created using a small quantity of water (2ml) and fruit flavourings OraSweet (19ml) and OraPlus (19ml).

The SPC proposal for a suspension is for use of 10 x 50mg EU formulation tablets in 10ml water and 95ml each of OraSweet and OraPlus. This proposed formulation can be considered as interchangeable with that used in the bioequivalence testing.

**Ingredients in the suspension**
Neither OraSweet or OraPlus are approved for use in any UK formulation under these US tradenames. However, there is considerable published literature on their use in the US and Canada as a 1:1 OraSweet/OraPlus combination. It is used as a suspending agent for a range of actives including sotalol, nifedipine and amlodipine.

The exact quantitative formulations of OraSweet, OraSweet sugar-free and OraPlus are not specified, but qualitative formulations are given in the application text for OraSweet SF and OraPlus. The formulation for OraSweet is not supplied by the applicant but is available on the manufacturer`s website: (http://www.paddocklabs.com/forms/msds/orasweet-1-02.pdf).

These commercial mixtures contain the preservatives/stabilisers potassium sorbate, methylparabens and propylparabens. The other ingredients sucrose, sorbitol, cellulose,

carrageenan, citric acid, glycerine, xanthan gum and flavourings are all known and accepted excipients.

Appropriate warnings should be included on the PIL about the presence of sorbitol in the suspension.

It should be noted that a suspension in OraSweet alone was not adequately physically stable to maintain the suspension. Therefore, it appears that the exact suspension formulation used may have a significant influence on stability and possibly bioavailability. Thus, results generated using this suspension cannot necessarily be applied to any other suspension using different suspending agents.

**Specification of the suspension**

An adequate specification is supplied for the suspension. Limits are applied to control the parameters of active substance content, degradation products, preservative concentration, appearance, pH and dissolution.

Stability indicating assay methods have been developed to assay the active and preservatives. These methods have been fully validated including linearity, accuracy, precision, sensitivity and intermediate precision.

The limits for assay are acceptable. The limits for named degradation products are also acceptable, but a limit other unknown impurities should be applied.

The limits for pH and dissolution are acceptable.

The limits for preservatives are wide:

Potassium Sorbate
Methylparaben
Propylparaben

This is not unusual, but the microbiological efficacy of the lower limit should be confirmed since the batches used in the stability and micobiological testing programme contained >> more than these lower limits.

**Stability**

Three batches of suspension were sampled at weekly intervals for 4 weeks. The parameters of active substance content, degradation products, preservative concentration, appearance, pH and dissolution were monitored. No time-related trends were observed in any of these parameters.

The photostability of the suspension was confirmed by a challenge with 1.2 million lux-hour of visible light and 200 W.hours/sq metre of UV light. No degradation of the active was observed and no new peaks were seen.

The microbiological challenge test was carried out according to USP chapter 51. This challenge test is comparable to the official Ph.Eur method. The suspension passes this USP test.

These data support the conclusion that a 1:1 OraSweet/OraPlus suspension is chemically and microbiologically stable for up to 4 weeks in a refrigerator at 2 – 8$^{o}$C.

**Bioequivalence of tablets and suspension**

Study P216 was an open label randomised two-period crossover study to investigate the bioequivalence of the above suspension and 50mg tablets in adults. The use of adults as a model is an acceptable compromise that does not alter the validity of this study.

The sample size of 16 subjects was adequate. Blood level sampling consisted of blank and 30 actual samples taken over a 36 hour period. This was quite adequate in duration and to characterise the peak.

The assay method was validated for a linear range of 1.0ng/ml to 500ng/ml. It is assumed that individual results obtained outside this range were obtained using a validated dilution technique but this should be confirmed for any pivotal studies.

**Pharmacokinetic parameters from Study P216**

| Parameter **Losartan** | Suspension | Tablet | Mean Ratio (Suspension/Tablet) | 90% Confidence Interval |
|---|---|---|---|---|
| AUC (ng.h/ml) | 366 | 395 | 0.927 | 83.4 – 103.1% |
| Cmax (ng/ml) | 208 | 174 | 1.195 | 98.4 – 145.0% |
| **Metabolite L-158641** | | | | |
| AUC (ng.h/ml) | 1814 | 1787 | 1.015 | 91.2 – 112.9% |
| Cmax (ng/ml) | 219 | 211 | 1.038 | 91.0 – 118.4% |

The pharmacokinetic results of this study suggest that this suspension is bioequivalent to the tablet formulation in terms of total availability. However, the Cmax confidence interval (98.4 – 145%) does not meet the standard ICH criteria for equivalence.

It must be stressed that these results are only relevant to the specific suspension used in study P216.

**Pharmacokinetics in the paediatric population**

Study P225 was a multicentre open label study to investigate the pharmacokinetics of multiple doses of Losartan in paediatric patients.

The sample size of 47 subjects in four age bands was adequate. The subjects received 6 – 15 doses. This should be adequate to produce steady state levels in all subjects.

Blood level sampling consisted of 10 samples taken over a 32 hour period. This was quite adequate in duration and to characterise the peak.

The assay method was validated for a linear range of 1.0ng/ml to 500ng/ml. It is assumed that the few individual results obtained outside this range were obtained using a validated dilution technique but this should be confirmed for any pivotal studies.

**Pharmacokinetic parameters from Study P225**

| Parameter | Group I Infants & Todlers | Group II Preschool children | Group III School age children | Group IV Adolescents |
|---|---|---|---|---|
| Number & Mean age | 9<br>1.1 years | 13<br>3.7 years | 11<br>9.0 years | 14<br>14.8 years |
| **Losartan** | | | | |
| AUC (ng.h/ml)* | 245 | 315 | 251 | 303 |
| Cmax (ng/ml) | 66.6 | 89.8 | 98.7 | 105.1 |
| Half Life (h) | 1.93 | 2.37 | 2.18 | 2.41 |
| **Metabolite L-158641** | | | | |
| AUC (ng.h/ml)* | 1457 | 951 | 1164 | 1590 |
| Cmax (ng/ml) | 147 | 91.5 | 139 | 188 |
| Half Life (h) | 4.8 | 5.6 | 5.4 | 5.7 |

* AUC 0-24hour used since this is a multiple dose study.

Groups I and II were treated using the unlicensed US suspension described in section 1.1. These results are only applicable directly to that suspension. Groups III and IV were treated with US tablet formulations. However, the formulation differences between the US and UK tablets are trivial.

The results of this study suggest that the AUC and Cmax values for losartan are similar across the age ranges. When results are corrected to a constant dose of 0.7mg/kg body weight the adolescent group have statistically significantly higher corrected AUC and Cmax values than do the infant & toddler group. This finding must be viewed with caution since it is the result of a multiple statistical testing of all four groups against each other. There is no consistent trend across the four groups

The elimination half life values are similar across the age ranges and were not statistically significantly different across any combination of the four age groups.

*This study supports the view that any age-related differences in absorption and elimination of losartan are considerably smaller than the normal random inter-individual variability between patients. Therefore, treatment using a dosing regimen of 0.7mg/kg body weight across all paediatric groups is supported by this evidence.*

**Pharmaceutical Assessor**