Public Assessment Report

Scientific discussion

Losartankalium/Hydrochlorthiazid "Liconsa"
Tarnasol Plus
Licolos Plus

Losartan Potassium /Hydrochlorothiazide

DK/H/1025-1027/001-002/DC

This module reflects the scientific discussion for the approval of Losartankalium/hydrochlorthiazid "Liconsa", Tarnasol Plus and Licolos Plus. The procedures were finalised on 9 January 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This report concerns three decentralised procedure applications for a generic version of losartan potassium/hydrochlorothiazide according to Article 10(1) of Directive 2001/83/EC (generic application).

With Denmark as the Reference Member State in these decentralised procedures, Liconsa S.A. is applying for the Marketing Authorisation of Losartan Potassium/Hydrochlorothiazide film-coated tablets 50/12.5 mg and 100/25 mg in:

- Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Luxemburg, Latvia, Norway, Sweden and the UK (DK/H/1025/001/002/DC).
- Czech Republic, Denmark, Estonia, Lithuania, Poland and Slovakia (DK/H/1026/001-002/DC).
- The Netherlands, Portugal and Slovenia (DK/H/1027/001-002/DC).

Based on the review of the data on quality, safety and efficacy, these applications for Losartan Potassium/Hydrochlorothiazide in the treatment of:

- Essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy (50 mg/12.5 mg film-coated tablets)
- Essential hypertension in patients whose blood pressure is not adequately controlled by losartan 50 mg/ hydrochlorothiazide 12.5 mg once daily (100 mg/25 mg film-coated tablets)

have been accepted by the RMS and all CMS. The list of follow-up measures can be found in section V of this report.

The originator product is Cozaar 50/12.5 mg film-coated tablets from Merck, Sharp & Dohme registered in Sweden since 20 March 1996.

Losartan is an orally active angiotensin II receptor (type AT_1) antagonist.

Therapeutic indications:
50 mg/12.5 mg film-coated tablets: For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

100 mg/25 mg film-coated tablets: For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by losartan 50 mg/ hydrochlorothiazide 12.5 mg once daily.

Posology:
50 mg/12.5 mg film-coated tablets: The usual starting and maintenance dose is 1 tablet once daily for most patients. For patients who do not respond adequately, the dosage may be increased to 2 tablets once daily. The maximum dose is 2 tablets once daily.

100 mg/25 mg film-coated tablets: The combination of 100 mg losartan potassium / 25 mg hydrochlorothiazide is not recommended as initial therapy. One losartan potassium / hydrochlorothiazide tablet once daily is recommended for those patients who do not respond adequately to a combination of 50 mg losartan potassium / 12.5 mg hydrochlorothiazide given once daily.

Losartan potassium/Hydrochlorothiazide may be administered with or without food.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For the manufacturing site within the Community, the RMS has accepted copies of current manufacturer authorisations issued by the inspection services of the competent authority as certification that acceptable standards of GMP are in place at this site.

II. QUALITY ASPECTS

II.1 Introduction

The general impression of the documentation is that it has been satisfactorily elaborated and justified in accordance with relevant guidelines.
The application is straight forward with no major scientific challenges in the quality part of the dossier. The active substances are chemical derived molecules. Losartan potassium can exist in different polymorphic forms. Both active substances have been shown to be stable. The medicinal product is formulated as film-coated tablets which are manufactured by conventional techniques using well-known excipients and packaging materials. The film-coated tablets seem to be quite stable.
The finished product is yellow round film-coated tablets to be marketed in Aluminum/PVC/PE/PVDC blisters. The excipients are microcrystalline cellulose, pregelatinised maize starch, lactose monohydrate, magnesium stearate, hydroxypropylcellulose, hypromellose, titanium dioxide and yellow iron oxide.

II.2 Drug Substance

The EDMF procedure has been followed for the active substance losartan and a letter of access has been submitted to the DMA.
Losartan potassium is manufactured in three steps. It is shown that polymorphic Form I is formed during the synthesis. Two of the starting materials are considered complex molecules and the ASM has therefore provided further information regarding the synthesis.
Points about characterisation and isomerism have been clarified. A point regarding potential content of catalyst has been clarified.
The proposed specifications for impurities in the active substance are almost in accordance with EU/ICH Q6A and Q3A guidelines. The specifications comply with the USP monograph on Losartan Potassium.
The analytical methods used for the active substance are for the most part satisfactorily described and validated in accordance with the relevant EU/ICH guidelines on *Analytical validation*.
The USP CRS is used. Information about source and characterisation of CRS impurities and certificates of analysis have been provided.
Losartan potassium is a stable molecule. Stability studies according to the relevant EU/ICH stability guidelines have been submitted. Significant changes are not observed at ICH conditions (up to 9 and 6 months). Therefore, a proposed extrapolation of the retest period to 15 months with no restrictions for storage is accepted.

Hydrochlorothiazide is submitted as a CEP. A re-test period of 5 years is approved according to the CEP.

II.3 Medicinal Product

The film-coated tablets are formulated with well-known excipients.
Information regarding justification for choice of dissolution testing parameters and compatibility with excipients has been included in the pharmaceutical development work.
Justifications for the choice of manufacturing process and packaging material are acceptable.

The manufacturing process has been satisfactorily described and validated in accordance with the EU guidelines on Manufacture of the finished dosage form and Process validation. The manufacturing process is conventional using standard techniques. Information about testing frequencies for in-process controls and holding times for bulk products has been provided.

Excipients comply with Ph. Eur. or EU regulations 95/45 (E 172). The only excipient derived from animal source is lactose monohydrate. It is confirmed that the preparation of lactose monohydrate is in accordance with the EU regulations.

The proposed limits on degradation products are justified according to the EU/ICH Q3B guideline. Other requirements are justified according to relevant EU/ICH guidelines and Ph. Eur.
The analytical methods used for the active substance are satisfactorily described and validated in accordance with the relevant EU/ICH guidelines.

The description and choice of container closure system is in accordance with relevant EU guidelines. The experience with the active substance and the data from the stability studies performed with the film-coated tablets shows that the chosen Aluminium-PVC/PE/PVDC blister adequately protects the product.

The film-coated tablets are stable at real-time and intermediate conditions, while significant changes in the content of degradation products originating from hydrochlorothiazid are observed at accelerated conditions. The studies have been carried out according to relevant EU/ICH stability guidelines. 3 batches per strengths have been stored for 18 and 24 months respectively. Extrapolations of the shelf-lives to 2 years respectively are acceptable with reference to the EU stability guideline for existing products. The proposed storage restriction "Do not store above 30°C" is acceptable. The product has been shown not to be photosensitive.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Losartan potassium and hydrochlorothiazide are well known. As the substances are widely used and well-known, the applicant has not provided additional studies and none are required as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended. An overview based on a literature review is therefore appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

No specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate. The clinical overview refers 12 publications up to year 2005.

The PSUR cycle will follow the PSUR synchronisation scheme agreed for losartan and hydrochlorothiazide and PSURs will be submitted every 3 years. The next PSUR will be submitted with DLP 2010/02.

IV.2 Pharmacokinetics

Losartan is an orally active angiotensin II receptor (type AT_1) antagonist. It undergoes substantial first-pass metabolism by cytochrome P450 enzymes, mainly 2C9 and 3A4. Losartan and its principal active metabolite Losartan carboxy acid block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the receptors. The active metabolite is 10 to 40 times more potent by weight than Losartan and appears to be a reversible non-competitive inhibitor of the AT_1 receptor.

Following oral administration, Losartan is well absorbed with a systemic bioavailability of approx. 33%. Both Losartan and its active metabolite are highly bound (about 99%) to plasma proteins, primarily albumin. The volume of distribution is 34 litres. Approximately 14% of an orally

administered dose is converted to the active metabolite. Mean peak concentrations of Losartan and its active metabolite are reached in 1 hour and in 2-4 hours, respectively.

C_{max} for both Losartan and the active carboxylic acid metabolite is approximately the same, whereas the AUC of the metabolite is about 4 times greater than that of Losartan. The main excretion pathway is through faeces and urine.

The pharmacokinetics of Losartan and its active metabolite are linear in oral doses up to 200 mg and do not change over time. Neither Losartan nor the active metabolite accumulates in plasma upon repeated once-daily dosing. Plasma concentrations decline polyexponentially with a terminal $t_{½}$ of approx. 2 hours for Losartan and approx. 6-9 hours for the carboxylic acid metabolite.

There is no clinically significant effect on the plasma concentration of Losartan when the drug is administered with a standardised meal.

Plasma concentrations of Losartan and the carboxy acid metabolite are 5-fold and 1.7-fold greater in patients with mild to moderate cirrhosis of the liver than in healthy volunteers. AUC for Losartan is doubled in haemodialysis patients.

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. Although the rate and extent of absorption have been reported to vary depending on the formulation administered, no studies have been performed to determine the clinical importance (if any) of variations in absorption in patients receiving chronic hydrochlorothiazide therapy. It appears to be preferentially bound to red blood cells. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is distributed into breast milk. Based on determination of plasma drug concentrations over a period of at least 24 hours, the plasma half-life of hydrochlorothiazide reportedly ranges from 5-15 hours. Hydrochlorothiazide is apparently not metabolised and is excreted unchanged in urine. At least 61% of the drug is reportedly eliminated from the body within 24 hours.

Bioequivalence
To support the application, the applicant has submitted one single dose bioequivalence study, performed with the 100/25mg strength.
A single dose study performed under fasting conditions is acceptable given that this is an immediate release product.

Biowaiver
The bioequivalence studies were performed using the 100/25mg strength tablets.
A justification for the biowaiver for the 50/12.5mg strength has been provided (in Module 2.3) on the basis that the conditions for bio-waivers in section 5.4 of the Bioequivalence guideline have been fulfilled (same manufacturer and process, linear pharmacokinetics, same qualitative composition, same ratio between active and excipients, comparable dissolution profiles of the strengths). The biowaiver conditions are considered to be satisfactorily fulfilled.

Study design
The study was a laboratory blind, randomized, single dose, two-way crossover study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 100/25mg was administered in each period with 200ml low carbonated water. Subjects were confined to the clinical research centre from at least 12 hours prior to drug administration until 24 hour post-dose in each period.

Methods of analysis:
Blood sampling performed predosing and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post-dose in each period. Samples were analysed by HPLC with tandem MS detection.

The design of the study is considered adequate, as intra-individual variation is not excessive, kinetics are linear and there are no overt signs of problems with assay sensitivity. The sampling period of 48 hours is sufficient to characterize the plasma concentration-time profile for each analyte based on half-lives of 2, 9 and 15 hours for losartan, losartan carboxy acid and hydrochlorothiazide respectively. The wash-out period of 7 days is long enough, based on data from the literature on the elimination rate of Losartan, its metabolite and hydrochlorothiazide, to avoid any carry over effect to the second period. It is acceptable that the study is conducted under fasting conditions to provide greater sensitivity, though the SPC indicates that the product may be administered with or without food.

The carboxy acid metabolite is measured in addition to the parent compound which is considered justified since the metabolite contributes significantly to the effect of the drug.

The study was conducted in accordance with GCP, local regulatory requirements and the Declaration of Helsinki.

Test and reference products
Losartan Hydrochlorothiazide 100/25mg tablets by Liconsa S.A. (batch No. LOHZR0501, batch size 120,000 tablets, DOM 08/2005) has been tested against Fortzaar 100/25mg tablets, Merck Sharp & Dohme (batch No 74890, from the Spanish market, exp. date 08/2004).

Satisfactory certificates of analysis of the test and reference product are presented in appendix 6 of the clinical study report (assay: Test: 99.2mg/24.7mg and reference: 98.0mg/24.6mg).

The compositions of the test and reference products are qualitatively similar. Detailed information on the test formulation is found in module 3.

The required information on the test and reference product is given. The application concerns 50/12.5mg and 100/25mg tablets proposed for marketing. The selection of the 100 mg strength for the bioequivalence study is considered appropriate from a pharmaceutical and clinical point of view. See the comments on acceptance of biowaivers above. The size of the test batch is $1/10^{th}$ that of the maximum proposed commercial batch size (1,200,000 tablets) and therefore acceptable in accordance with the BABE guideline.

Population(s) studied
48 healthy volunteers were randomised into the study and 48 completed (20 female/20 male, 18-40 years, 50-91kg, Caucasian). No smoking was permitted. There were no drop-outs.
The population is mixed male/female and acceptable. The number of subjects included in the study is considered sufficient to obtain a power of at least 80% to conclude bioequivalence reliably with an alpha level of 0.05.

Analytical methods
The blood samples were analyzed for Losartan and Losartan carboxy acid by HPLC with MS/MS detection, using valsartan as internal standard. Initial validation was performed in July 2005 for losartan and its metabolite and subsequently revalidated at various times thereafter in response to modifications in analytical instruments employed, to ensure optimised extraction and separation of the peaks, and to ensure lack of interference from hydrochlorothiazide. A chronology is provided at the beginning of Module 5, Vol. 3 of 10. An analytical validation report, LOS_BE_LCMSMS-01/05, revision 5.0, dated 25th July 2006 has been provided. The method is shown validated within a range of 7.500ng/ml-1920.000ng/ml for both Losartan and Losartan carboxy acid. Dilution integrity is acceptable up to 4-fold. Losartan and metabolite have been shown to be stable in plasma samples following 3 freeze-thaw cycles, for up to 6 months stored below -20°C, for 1 month stored at -80°C, and for up to 16 hours at room temperature (20°C).

For hydrochlorothiazide analysis, a separate HPLC/MS/MS analytical method has been employed using chlorothiazide as internal standard and shown validated within a range of 1.000ng/ml-243.000ng/ml. Dilution integrity is acceptable up to 4-fold and hydrochlorothiazide has been shown to be stable in plasma samples for up to 4 months stored below -20°C, following 3 freeze-thaw cycles,

and for up to 3 hours at room temperature (20°C). Extracted samples are also stable for up to 12 hours at RT and for up to 24 hours at -20°C. The method has been validated for lack of interference from losartan, losartan carboxy acid and lisinopril.

Separate bioanalytical reports dated 3rd August 2006 and 28th July 2006 have been provided for analysis of hydrochlorothiazide and losartan and its metabolite respectively.

Date of start and finish of the bio-analytical phase:
The study samples were analysed from 6th July to 23rd July 2006 for losartan and losartan carboxy acid; the maximum sample storage period from the first blood draw was 64 days.

The study samples were analysed from 26th July to 2nd August 2006 for hydrochlorothiazide; the maximum sample storage period from the first blood draw was 74 days.

Reanalysis of samples: A total of 2208 plasma samples were analysed of which 7 were reanalysed for losartan and metabolite as samples were not injected properly. 10 sequences were repeated as calibration and QC samples were outside acceptance limits and a further 4 due to instrument failure. For hydrochlorothiazide, 3 samples were repeated as the concentrations exceeded the calibration curve. 10 sequences were repeated as calibration and QC samples were outside acceptance limits and a further 4 due to instrument failure.

The analytical method has been satisfactory validated (pre-study and within study) and the handling of samples is adequate. Plausible reasons are presented for analysis repetition.

Pharmacokinetic Variables
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, MRT and % extrapolated AUC.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for losartan and hydrochlorothiazide
Secondary parameters: t_{max}
Information parameters: $t_{½}$, MRT, % extrapolated AUC for losartan and hydrochlorothiazide and AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, MRT and % extrapolated AUC for losartan carboxy acid.
PK variables were measured for both Losartan and its active metabolite Losartan carboxy acid.

The pharmacokinetic variables evaluated are considered adequate. The carboxy acid metabolite of losartan is evaluated in addition to the parent compound for information which is considered appropriate as the metabolite contributes significantly to the overall effect of the product.

Statistical methods
ANOVA was performed on the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The ANOVA model included sequence, subject nested within sequence, period and product. Confidence intervals were calculated according to Classic and two one-sided t-testing was performed according to Schuirmann at a 5% level of significance. Non-transformed T_{max} was evaluated using Wilcoxon and Kruskall-Wallis testing

Bioequivalence criteria:
90% geometric intervals of the ratio (A/B) of least square means from the ln-transformed values for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} should be within 80-125%. Safety parameters were descriptive only.

The statistical methods have been adequately described and are acceptable. All statistical calculations were performed using SAS version 9.1. The protocol required 44 subjects to complete the trial. As 48 completed and were evaluated, the statistical requirements are met and the results are considered valid.

There were no major protocol deviations. Minor deviations occurred with subjects 4, 23, 32 and 38 who did not finish their allocated meal. The deviations were not considered to have impact on the overall outcome of the study outcome.

Results

Table 1 - Losartan:

Parameters	***Test*** **Mean (%)**	**±**	**SD**	**CV**	***Reference*** **Mean (%)**	**±**	**SD**	**CV**
AUC_{0-t} (ng/ml*h)	840.646	±	399.178	47.485	843.308	±	410.928	48.728
AUC_{0-inf} (ng/ml*h)	883.169	±	400.533	45.352	884.753	±	416.492	47.074
C_{max} (ng/ml)	526.937	±	301.289	57.178	536.284	±	329.968	61.529
T_{max} (h)	1.443	±	0.968	67.099	1.308	±	0.784	59.970

	AUC_{0-t}	**AUC_{0-inf}**	**C_{max}**
Ratio	100.304%	100.679%	100.153%
90% geometric Confidence interval	96.179% - 104.606%	96.782% - 104.732%	86.938% - 115.375%

Schuirmann Test:

	Test value	**Lower t**	**Upper t**
AUC_{0-t}	1.679	8.799	9.041
AUC_{0-inf}	1.679	9.202	9.778
C_{max}	1.679	2.629	2.665

Table 2 – Hydrochlorothiazide:

Parameters	***Test*** **Mean (%)**	**±**	**SD**	**CV**	***Reference*** **Mean (%)**	**±**	**SD**	**CV**
AUC_{0-t} (ng/ml*h)	1085.254	±	295.726	27.249	1050.916	±	260.520	24.790
AUC_{0-inf} (ng/ml*h)	1114.855	±	297.600	26.694	1085.285	±	265.805	24.492
C_{max} (ng/ml)	141.547	±	42.121	29.758	131.225	±	36.669	27.943
T_{max} (h)	2.818	±	1.289	45.738	3.069	±	1.285	41.879

	AUC_{0-t}	**AUC_{0-inf}**	**C_{max}**
Ratio	102.582%	102.110%	107.249%
90% geometric Confidence interval	98.386% - 106.956%	98.108% - 106.274%	101.639% - 113.169%

Schuirmann Test:

	Test value	**Lower t**	**Upper t**
AUC_{0-t}	1.679	7.945	9.994
AUC_{0-inf}	1.679	8.493	10.247
C_{max}	1.679	4.785	9.158

Table 3 – Losartan carboxy acid:

Parameters	***Test*** **Mean (%)**	**±**	**SD**	**CV**	***Reference*** **Mean (%)**	**±**	**SD**	**CV**
AUC_{0-t} (ng/ml*h)	5145.084	±	2019.654	39.254	4956.134	±	1890.316	38.141
AUC_{0-inf} (ng/ml*h)	5262.595	±	2029.109	38.557	5072.221	±	1911.863	37.693
C_{max} (ng/ml)	854.288	±	317.399	37.154	830.800	±	345.232	41.554
T_{max} (h)	2.974	±	1.209	40.640	3.079	±	1.334	43.336

	AUC_{0-t}	**AUC_{0-inf}**	**C_{max}**

Ratio	103.232%	103.255%	104.172%
90% geometric Confidence interval	99.579% - 107.018%	99.593% - 107.051%	99.310 - 110.407%

Schuirmann Test:

	Test value	**Lower t**	**Upper t**
AUC_{0-t}	1.679	8.917	11.881
AUC_{0-inf}	1.679	8.886	11.864
C_{max}	1.679	5.613	8.531

Intra-subject variability coefficients were calculated for all primary parameters as follows:

	AUC_{0-t}	**$AUC_{0-\infty}$**	**C_{max}**
Losartan	12.256%	11.519%	41.294%
Hydrochlorothiazide	12.188%	11.667%	15.680%
Losartan carboxy acid	10.512%	10.537%	15.458%

The extrapolated AUC is below 20% in each individual subject (100mg study: average 5.2% for reference and 5.6% for test. No pre-dose levels of losartan, hydrochlorothiazide or losartan carboxy acid were observed in either of the two periods, i.e. the wash-out period is adequate. No subjects reached C_{max} at the first sample time indicating that the sampling scheme was adequate. ANOVA detected no period or sequence effects though subject in sequence effect was significant for all three primary parameters for losartan, metabolite and hydrochlorothiazide. The applicant comments that subject effects are frequently observed due to inter-individual variations and do not affect the validity of the study. The RMS concurs. A treatment effect was recorded for C_{max} for hydrochlorothiazide (p=0.0339). Schuirmann testing indicates no significance difference between the products for any primary parameter.

The 90% confidence intervals for the ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the acceptance range of 80-125% for Losartan, hydrochlorothiazide and the metabolite Losartan carboxy acid. Calculated intra-subject variabilities are reasonably low apart from C_{max} for losartan.

Acceptable plasma concentration-time curves (linear-linear and log-linear) are presented.

Safety evaluation:
No serious adverse events were reported during the study. 9 adverse events (nausea, dizziness and vomiting) were reported by 6 subjects of which 8 were mild and one of moderate intensity. The most commonly reported adverse event was nausea (4 cases). All adverse events were assessed as related to study medication, 7 probably and 2 possibly. Two thirds of the AEs were attributed to test treatment.

ANOVA of clinical laboratory parameters follow-up versus screening shows statistically significant differences for lower values of haemoglobin, red blood cells, haematocrit, neutrophils, bilirubin, calcium, cholesterol and glucose and higher values for lymphocytes, white blood cells and sodium. ANOVA also detected differences regarding lower values results for systolic and diastolic blood pressure and heart rate at follow-up versus screening though all statistical difference are clinically insignificant.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study, Losartan potassium/Hydrochlorothiazide Liconsa 50/12.5mg and 100/50mg tablets are considered bioequivalent with Cozaar Comp/Fortzaar tablets. Tolerability of the test product is acceptable and not significantly different from reference product.

Dissolution studies:

Comparative in-vitro dissolution data have been generated for the test and reference products using the following dissolution conditions:

Apparatus	: apparatus II (paddles)
Temperature	: 37°C+/-0.5°C
Rpm	: 100 rpm
Dissolution medium	: Phosphate buffer pH 6.8
Volume	: 900 ml
Sampling times	: 5, 10, 15, 20, 30, 45 and 60 minutes

Both test and reference products had >85% losartan dissolved within 20 minutes and approx. 80% hydrochlorothiazide dissolved within 80%. Similarity factors (f_2) were calculated at 83.47 for losartan and 64.84 for hydrochlorothiazide indicating similarity between the test and reference products.

The BE batches have also been compared using 0.1N HCl and phosphate buffer pH 4.5. The profiles obtained were not significantly different.

Test product 50/12.5mg and 100/50mg product have also been compared using the above dissolution conditions and acceptable f_2 values calculated indicating similarity of the two test strengths.

Reference is made to Module 3 for additional information.

The composition of the batch used for BE studies is identical to the product applied for.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Losartan Potassium/Hydrochlorothiazide film-coated tablets 50/12.5 mg and 100/25 mg are generic medicinal products with losartan potassium and hydrochlorothiazide as the active ingredients. The quality documentation has been satisfactorily elaborated and justified in accordance with relevant guidelines. Bioequivalence with the originator product Cozaar Comp. has been demonstrated. The efficacy and safety aspects of losartan potassium and hydrochlorothiazide are well described and the SPC adequately reflects the characteristics of the product. Both from a quality, non-clinical and clinical point of view the benefit risk assessment is considered positive.

The following commitments have been made during the procedure:

- The EDMF is acceptable provided that the issue regarding use of catalysts is resolved with the following conditions:

  Batch analyses for 2-(1-methyl-1-phenylethyl)-5-phenyl-2H-tetrazol will be submitted when available and these data will be included in the next updated EDMF.

  A re-test period of 15 months is maintained. A precondition is that the stability study on the production batch TK0 5003 is commenced and that results from the study is forwarded to the RMS as soon as data are available.

  It is confirmed by the ASM that a complete revised version of the EDMF will be prepared, including all the necessary amendments, when the evaluation of the EDMF in relation to all decentralized procedures will be finished. Furthermore, the respective Open Part will be sent to the Applicant.

- The applicant commits to perform validation of the manufacturing process (of all applied strengths) on the first three industrial scale batches (maximum batch size) manufactured at proposed manufacturing site, including fixing of operating parameters in detail and validation of the

uniformity of content. A validation report should be available on request no later than one year from the date of the issued marketing authorisations.

- The applicant commits to submit an up-dated description of the manufacturing process relating to mixing times for batches sizes larger than already manufactured as soon as the relevant process validation data are available.

- The proposed shelf-life of 2 years with the storage condition "Do not store above 30°C" are accepted for both strengths. A precondition is that stability results covering 2 years storage for the 50/12.5 mg strength will be forwarded to the RMS and CMSs when available and no later than March 2008.

- The first 3 production scale batches of the product of all dosage strengths will be put on stability and tested according to the stability protocol as presented in section P.8.1.

- The applicant commits to adapt the SPC and PL in accordance with the outcome of the Article 30 harmonisation of Cozaar and Cozaar Comp EMEA/H/A-30/835.