National Institute of Pharmacy
Directorate of GYEMSZI
Budapest, Hungary

Public Assessment Report Numbers:
HU/H0268-0271/001-002/DC

Public Assessment Report

Scientific discussion

Names of the Products:

Eridanus 25mg and 50mg film-coated tablets[1]
Licepler 25mg and 50mg film-coated tablets[2]
Raasblock 25 mg and 50mg film-coated tablets[3]
Eplerone Liconsa 25 mg and 50mg film-coated tablets[4]

eplerenone

Procedure numbers:

ERIDANUS 25 mg film-coated tablet	HU/H/0268/001/DC
ERIDANUS 50 mg film-coated tablet	HU/H/0268/002/DC
LICEPLER 25 mg film-coated tablet	HU/H/0269/001/DC
LICEPLER 50 mg film-coated tablet	HU/H/0269/002/DC
RAASBLOCK 25 mg film-coated tablet	HU/H/0270/001/DC
RAASBLOCK 50 mg film-coated tablet	HU/H/0270/002/DC
EPLERENONE LICONSA 25 mg film-coated tablet	HU/H/0271/001/DC
EPLERENONE LICONSA 50 mg film-coated tablet	HU/H/0271/002/DC

Applicants:

[1,]**Gedeon Richter Plc.**
[2,3,4]**Laboratorios Liconsa S.A**

Date: 24 July 2012

This module reflects the scientific discussion for the approvals of ERIDANUS, LICEPLER, RAASBLOCK and EPLERIUM 25-50 mg film-coated tablets.
The procedure was finalised at: 11 April 2011
For information on changes after this date please refer to the module 'Update'

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I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS:)

- *Eridanus*: Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Poland, Romania, Slovakia,
- *Licepler*: Greece,
- *Raasblock*: Austria, Spain,
- *Eplerone Liconsa*: Bulgaria, Czech Republic, Greece, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

concerned the generic version of eplerenone 25 and 50 mg film-coated tablets. It was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The products have been developed by Gedeon Richter Plc. The originator product Inspira® from Pfizer has been authorised for marketing in Europe since 2004.
Eplerenone is indicated as additional medication to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction. The maximum daily dose is 50 mg per day.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for the submitted eplerenone products.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Eridanus, Licepler, Raasblock and Eplerenone Liconsa 25 and 50 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Gedeon Richter Plc. The reference products are Inspra 25 and 50 mg film-coated tablets (containing 25 or 50 mg eplerenone as active ingredient) which were the original products of Pfizer Inc.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's dossier using the Active substance Site Master File (ASMF) procedure. The Quality Overall Summary is adequate.

INN name: eplerenone.

Chemical name: 9α,11α-Epoxy-17β-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone 7-methyl ester.

The active substance is a white, almost white or slightly yellow crystalline powder. It is freely soluble in dichloromethane, slightly soluble in methanol and water. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder supplied complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, TG, XRDP, and DSC and by UV spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Eplerenone is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification by IR and UV spectrophotometry, water content, sulphated ash, specific optical rotation, heavy metals, related substances, residual solvents, assay, polymorphic content and microbiological purity. The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the re-test period of 24 months is acceptable with no special storage condition.

GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop film-coated tablets containing eplerenone as drug substance in 25 and 50 mg doses, pharmaceutically and bioequivalent to the reference medicinal products Inspra 25 mg and 50 mg film-coated tablets, the branded original products of Pfizer.

A satisfactory package of data on development pharmaceutics has been presented. A brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product. A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The compositions and the dosage-form tests evaluated during development of the final formulation are included in the documentation.

As a result of development studies product with the following composition, appearance and packaging was obtained.

> The excipients used in the finished product are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium laurylsulfate, hypromellose, talc, magnesium stearate and opadry white (lactose monohydrate, macrogol, titanium dioxide and hypromellose). All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.
>
> Eplerenone 25 mg film-coated tablets are white or almost white, round, biconvex with diameter approximately 6 mm, one side engraved with CG3, other side without engraving.
> Eplerenone 50 mg film-coated tablets are white or almost white, round, biconvex with diameter approximately 8 mm, one side engraved with CG4, other side without engraving.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 2 years with no special storage conditions** is approved.

The Summary of Product Characteristics, Patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: the product has been demonstrating to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of eplerenone are well known. Claiming that the active pharmaceutical ingredient is a widely used well-known active substance the Applicant has not performed further studies. Therefore an overview based on literature review is acceptable.

III.2 Pharmacology

The Application is based on Article 10(1) of Directive 2001/83/EC (generic application). Pharmacodynamics of eplerenone is well-known. The non-clinical part, based on a literature review, of the application is acceptable.

III.3 Pharmacokinetics

The Application is based on Article 10(1) of Directive 2001/83/EC (generic application). Pharmacokinetics of eplerenone is well-known. The non-clinical part, based on a literature review, of the application is acceptable.

III.4 Toxicology

The Application is based on Article 10(1) of Directive 2001/83/EC (generic application). Toxicology of eplerenone is well-known. The non-clinical part, based on a literature review, of the application is acceptable.

III. 5 Ecotoxicity/environmental risk assessment

A suitable justification for the absence of an environmental risk assessment has been provided, stating that the use of the proposed generic product is unlikely to increase environmental exposure to the active substance.

III.6 Discussion on the non-clinical aspects

There is no objection against granting the marketing authorization from a clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This Decentralised Procedure application concerns the generic versions of eplerenone. The application is submitted according to Article 10(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC).

The claimed indication is:

Eplerenone is indicated, in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction.

The following posology is recommended:

The recommended maintenance dose of eplerenone is 50 mg once daily (OD). Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks, taking into account the serum potassium level. Eplerenone therapy should usually be started within 3-14 days after an acute myocardial infarction.

The claimed indication and posology are in line with those of the originator (reference product).

IV.2 Pharmacokinetics

Literature data

Absorption and Distribution:
The absolute bioavailability of eplerenone is unknown. Maximum plasma concentrations are reached after about 2 hours. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 10 to 100 mg and less than proportional at doses above 100 mg. Steady state is reached within 2 days. Absorption is not affected by food.

The plasma protein binding of eplerenone is about 50% and is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state is estimated at 50 (±7) L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and excretion:
Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and faeces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the faeces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 3 to 5 hours. The apparent plasma clearance is approximately 10 L/hr.

Bioequivalence study

In order to demonstrate bioequivalence with the reference product, one bioequivalence (BE) study was conducted by Lambda Therapeutic Research Ltd. (Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India) with Gedeon Richter plc. as sponsor between August 19 and 28 2008. The study utilised the higher dosage-forms (50 mg eplerenone). The conduct of the study is adequate, all parts were performed in compliance with GCP and GLP, local regulatory requirements and the principles enunciated in the Declaration of Helsinki, and the results comply with the acceptance criteria for bioequivalence as detailed in the relevant CHMP guideline (CPMP/EWP/QWP/1401/89).

Title
An open-label, balanced, randomized, single dose, two treatment, two period, two sequence, two way crossover bioequivalence study of two formulations of eplerenone 50 mg film-coated tablets in healthy, adult, human subjects under fasting conditions.

Design
It was a two period, single dose, two-way cross over study. Equal allocation to treatment sequence was assured as per the randomization schedule. The venous blood samples were withdrawn at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36.00 hours post dose in each period. Sample at 36 hour was collected on ambulatory basis. The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Professional Software Version 5.0.1 (Pharsight Corporation, USA) for eplerenone. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA) to assess the bioequivalence of eplerenone. Descriptive statistics was computed and reported for primary and secondary pharmacokinetic parameters for eplerenone.

Assessor's comment:
The study design is appropriate. The number of measurements around the C_{max} and the duration of sample-collection are sufficient. The wash-out period is long enough to exclude carry-over effects.

Population studied
- Planned enrolment: 24 subjects were to be enrolled and dosed in the study.
- Actual enrolment: A total of 26 subjects, including 2 extra subjects were checked-in for this study. The extra subjects were checked-in to account for any dropouts prior to dosing in Period-I. Out of these 26 subjects, 2 subjects (Subject Nos. 1021 and 1022) were females.
- As per the protocol, 24 subjects (Subject Nos. 1001-1024) were dosed in Period-I of the study. In all, 22 subjects (Subject Nos. 1001-1002, 1004-1020 and Subject Nos. 1022-1024) completed the clinical phase of the study. Blood samples of all the 22 subjects were analyzed.

Subject No. 1003 and 1021 were withdrawn on the grounds of protocol deviation. Subject 1003 had a positive urine drug test in check-in to Period II. Subject 1021 participated in another clinical study approximately 40 days before Period I.

Bioanalytics
The plasma samples of subjects were analysed using a validated LC-MS/MS method for eplerenone. The validated analytical range was 5.014ng/mL – 1493.598ng/mL for eplerenone. Spironolactone was used as internal standard.

A total of 961 study samples were received and analyzed. 47 samples were missing from the precalculated 1008. A total of 76 reanalyses were carried out in duplicates in the study due to the following reasons:

- 68 samples were reanalysed due to concentration above the highest standard.
- 5 samples were reanalysed due to significant variation in response of internal standard.
- 3 samples were reanalysed due to anomalous concentration.

Statistical methods
Descriptive statistics were computed and reported for primary and secondary pharmacokinetic parameters for Eplerenone.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for untransformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and un-transformed pharmacokinetic parameters, λ_z and $t_{½}$ were computed for Eplerenone.

The 90% parametric confidence intervals were calculated for the un-transformed and ln-transformed pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and un-transformed pharmacokinetic parameters, λ_z and $t_{½}$ of the Eplerenone.

Wilcoxon Signed Rank test was performed to assess the pharmacokinetic parameter T_{max}.

Bioequivalence of Test Product-B vs. Reference Product-A was concluded if the 90% confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Eplerenone.

The predefined acceptance criterion for the confidence interval of the C_{max} and AUC0-t ratios was between 80-125%.

Assessor's comment:
The statistical method and the bioequivalence criteria are acceptable.

Results

They are indicated in the following Tables (Table B and Table C).

The mean pharmacokinetic parameters of Eplerenone for Reference Product-A and Test Product-B for 22 subjects are summarised in the following tables.

Table B - Descriptive Statistics of Formulation Means for Eplerenone (n=22)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product-A	Test Product-B
T_{max} (h)*	1.750	1.500
C_{max} (ng / mL)	1490.167 ± 327.4937	1474.308 ± 317.0335
AUC_{0-t} (ng.h / mL)	9709.833 ± 3345.4908	9809.274 ± 3483.5544
$AUC_{0-\infty}$ (ng.h / mL)	9832.911 ± 3442.7753	9929.596 ± 3536.7264
λ_z (1 / h)	0.176 ± 0.0537	0.172 ± 0.0517
$t_{½}$ (h)	4.239 ± 1.0762	4.334 ± 1.1101
AUC_% Extrap (%)	1.132 ± 0.7737	1.188 ± 0.6646

*T_{max} is represented in median value.

Table C - Geometric least squares Mean, Ratios and 90% Confidence Interval for Eplerenone (n=22)

Parameters (Units)	(ln-transformed) Geometric least squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	Ratio (B / A)%	
C_{max} (ng / mL)	1442.908	1461.033	98.8	93.73 – 104.06%
AUC_{0-t} (ng.h / mL)	9290.531	9274.931	100.2	94.50 – 106.18%
$AUC_{0-\infty}$ (ng.h / mL)	9400.651	9382.173	100.2	94.44 – 106.31%

Assessor's comment:
The calculated confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of eplerenone are within the 0.80-1.25 acceptance range for bioequivalence. The other pharmacokinetic variables were comparable between the test product and the reference product.

Safety:
A total of 3 adverse events were reported by two subjects during the conduct of the study (dyspepsia, abdominal pain, vomiting).

Two adverse events occurred during the Period-I and one adverse events occurred in Period-II.

Two adverse events were reported in subjects receiving the test product and one adverse event was reported in subjects receiving the reference product. All the adverse events were mild in nature and were followed up till resolution. All the 3 adverse events were judged as possible related to the study drug.

There were no deaths reported during the course of the study. There were no serious or other significant adverse events in the study.

Assessor's comment:
No new safety concern emerged during the study. The safety profile of the test product is comparable with that of the originator.

Conclusion
The results of the bioequivalence study comply with the requirements of the CPMP/EWP/QWP/1401/98 Rev. 1. *Note for Guidance on the Investigation of Bioavailability and Bioequivalence.* Therefore essential similarity for the Applicant's product Eplerenone 50mg film-coated tablet and the originator Inspra® 50mg film-coated tablet is proven.

Biowaiver
The Applicant has requested a biowaiver to the 25mg strength of eplerenone. The claim is based on the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98. This guideline states that the biowaiver can be granted if the following criteria are all met:
- the pharmaceutical products are manufactured by the same manufacturer and process;
- the drug input has been shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used);
- the qualitative composition of the different strengths is the same;

- the ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

The first four criteria are met. The Applicant has provided the data of the comparative dissolution profile between the biobatch and the 25mg strength and also between the 25 mg strengths of the test and reference preparations at the three relevant pH values (see Quality section).

The Applicant could not prove the similar dissolution of the 25mg eplerenone with the 50mg biobatch at two pH values by the similarity factor of f2 >50. The 25 mg strength showed slightly more rapid dissolution than the biobatch at pH 4.5 and 6.8. However, the Applicant explained this phenomenon by stating that the differences are "rather drug substance related than formulation related". To support this, the Applicant submitted comparative dissolution data for both strengths of the test and reference preparations as presented in the Quality section.

Dissolution profiles of the 25 mg test and reference preparations were found to be similar at all the three pH values, just as those of the biobatch and the 50 mg reference product.

Assessor's comment:

Based on the similar dissolution behavior of the test and reference products including the demonstrated similarity of the corresponding strengths at all the three pHs and taking into consideration that

- the API dissolves from both strengths of the test product very rapidly at all the three pH values (80% or more in 15 minutes),
- dissolution of the API from the two strengths of test product is shown to be similar at the most acidic medium, which simulates the conditions in the stomach the best,
- the slightly faster *relative* dissolution of API from the lower strength at pH 4.5 and 6.8 cannot be expected to have any impact on bioavailability of the API and consequently to pose any safety and efficacy concerns, moreover, the same phenomenon could be observed for the reference tablets,

the biowaiver for the 25 mg strength of Eplerenone is regarded approvable.

IV.3 Pharmacodynamics

Eplerenone belongs to the group of aldosterone antagonists i.e. it prevents the binding of aldosterone, a key hormone in the renin-angiotensin-aldosterone-system to its receptors. Aldosterone receptors are mainly located in the upper region of the collecting tubules of the nephron and the hormone increases sodium and water reabsorption and in exchange potassium is excreted. By inhibiting aldosterone actions eplerenone increases sodium and water excretion and retains potassium. This effect is similar to that of spironolactone the well-known diuretic agent.

Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone.

Eplerenone has been proven to reduce both all-cause and cardiovascular mortality in postinfarction patients with heart failure (see EPHESUS study).

IV.4 Clinical efficacy

Since the clinical efficacy of eplerenone had already been proven and the present application was a "generic" one no specific clinical studies were performed.

IV.5 Clinical safety

The applicant has submitted one bioequivalence study.

No new safety concern emerged during the study. The safety profile of the test product is comparable with that of the originator.

IV.6 Discussion on the clinical aspects

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application concerns a generic version of eplerenone tablets. The suggested indicationin is in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40 %) and clinical evidence of heart failure after recent myocardial infarction. The active substance is widely and safely used, the application of the present product dose not pose any new risk.

The submitted documentation is formally adequate and scientifically sound. The benefit/risk assessment is positive. There is nothing against the marketing authorization.

V.1 Conditions for marketing authorization

V.1.1 Requirements for specific post-marketing obligations.

Not needed.

V.1.2 Pharmacovigilance system

The new version of the Pharmacovigilance system of Gedeon Richter PLC (Version 11.1 as of 12 January 2011) as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union.
The Applicant also provides adequate evidence that the proposed Marketing Authorization Holders

Gedeon Richter Plc. Budapest, Hungary
Gedeon Richter Romania SA Tg Mures, Romania
Gedeon Richter Polska Sp. z. o.o, Poland

have the services of a qualified person, responsible for pharmacovigilance and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Pharmacovigilance system (date of report: January 2010) as described by the Applicant fulfils the requirements and provides adequate evidence that the proposed Marketing Authorization Holder (LABORATORIOS LICONSA, S.A.) has the services of a qualified person, responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V.1.3 Risk Management Plan

The statement of applicant that a Risk Management Plan based on the Volume 9A of The Rules Governing Medicinal Products for Human Use in the European Union, Chapter 1.3 Section 4 (September 2008) is not required has been accepted.

V.1.4 Periodic Safety Update Report (PSUR)

In accordance with the aim of HMA (Heads of Medicines Agencies) Working Group on PSUR synchronisation, the Applicant would like to harmonise the product's PSUR cycle to the agreed EU harmonised birth day of eplerenone active substance (16 March 2004) and to the related Data Lock Point (DLP, March 2009). PSURs are intended to be submitted on a three-yearly basis. The intended first DLP is 31 March 2012. It has been accepted.

V.1.5 Legal status

Prescription-only medicine.

V.2 Summary of Product Characteristics (SmPC)

The SmPC is acceptable; it has been harmonized with that of the originator product.

V.3 Package leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The study included a pilot test with four subjects and two rounds of test with twenty users. The selection method was appropriate during recruitment.

The demographics and goal oriented selection of target population tested, the number of participants, the time aspects (length of interview), the face-to face technique of conducting of the interviews and Questionnaire were found appropriate during the two test periods.

Regarding to evaluation of interviews, the evaluation's system (*demonstration of data analysis of the testing procedure, actual conclusions based on post statistical analysis, bar charts*, etc) were appropriate and all in accordance the legal requirements of EU legalisation.

VI. UPDATE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Licepter: shelf life extension to 3 years	HU/H0269/001-002/IB/001	Y	30. 05. 2012	29. 06. 2012	Approval	N
Raasblock: change of product name and of the Pharmacovigilance system in Spain	HU/H/0270/001-002/IB/001/G	Y (in Spain)	07. 03. 2012	05. 04. 2012	Approved	N
Raasblock: shelf life extension to 3 years	HU/H/0270/001-002/IB/002	Y	30. 05. 2012	29. 06. 2012	Approved	N
Eplerone Liconsa: change of product name and of the Pharmacovigilance system in Spain	HU/H/0271/001-002(IBI001/G	Y (in Spain)	16. 05. 2012	15. 06. 2012	Approved	N
Eplerone Liconsa: shelf life extension to 3 years	HU=H=0271/001-002/IB/002	Y	30. 05. 2012	29. 06. 2012	Approved	N