CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Licolin 75 mg, 150 mg and 300 mg, tablets
Laboratorios Liconsa S.A., Spain

irbesartan

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1626/001-003/DC
Registration number in the Netherlands: RVG 104221-104223

16 November 2010

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA04
Route of administration:	oral
Therapeutic indication:	essential hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus
Prescription status:	prescription only
Date of authorisation in NL:	11 October 2010
Concerned Member States:	Decentralised procedure with AT, IE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Licolin 75 mg, 150 mg and 300 mg tablets, from Laboratorios Liconsa S.A. The date of authorisation was on 11 October 2010 in the Netherlands.

The product is indicated for:
- treatment of essential hypertension.
- treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen.

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

Irbesartan is a potent, orally active, selective angiotensin II receptor (type AT_1) antagonist. It is expected to block all the actions of angiotensin II mediated by the AT_1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT_1) receptors results in increases in plasma renin levels and angiotensin II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Karvea 75 mg, 150 mg and 300 mg tablets, which have been registered through the centralised procedure EU/1/97/049/001-039 by Bristol-Myers Squibb Pharma EEIG since 27 August 1997. Further information can be found in the EPAR of Karvea (http://www.ema.europa.eu/htms/human/epar/).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Karvea 300 mg, registered in the European Union. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

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

No paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

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

Active substance
The active substance is irbesartan, an established active substance described in the US Pharmacopoeia. (USP*). The active substance is insoluble in water at different pHs. In literature two polymorphic forms are known. Polymorphic form A is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured in a four step process. A flow chart and short description of the manufacturing process is included. Methanol and isopropyl alcohol are the solvents used during manufacturing. The structure of the drug substance has been adequately elucidated.

Quality control of drug substance
The drug substance specification is in line with the USP, with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for five production scaled batches and two pilot scaled batches stored at 25°C/60% RH (36 months data for four batches) and 40°C/75% RH (6 months). The polymorphic form does not change during storage. At accelerated storage conditions no changes were observed. At long term storage conditions only a slight increase in water content is seen after two or three years. The claimed re-test period of three years is justified, with no special storage condition. A photostability study revealed that the drug substance is photostable.

** USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

Medicinal Product

Composition
Licolin 75 mg contains as active substance 75 mg of irbesartan, and is a white, cylindrical, biconvex tablet.
Licolin 150 mg as active substance 150 mg of irbesartan, and is a white, cylindrical, biconvex tablet, scored on one side.
Licolin 300 mg as active substance 300 mg of irbesartan, and is a white, oblong, biconvex tablet, scored on one side.

The score line on the 150 and 300 mg tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are packed in white opaque PVC-PVDC/Aluminium blisters.

The excipients are: cellulose microcrystalline (E460), croscarmellose sodium (E468), lactose monohydrate, magnesium stearate (E572), silica colloidal anhydrous (E551), maize starch, povidone K-29/32 (E-1201), hydrogenated castor oil.

The different strengths are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The compatibility of the excipients with the drug substance is determined. Before preformulation the innovator product was studied with respect to packaging, appearance, weight, hardness, dimensions and disintegration.
The solubility of irbesartan at different pH's was investigated. The lower the pH, the better irbesartan dissolves. The dissolution profiles of innovator and test product were determined in 0.1N HCl. The dissolution profiles are comparable since > 85% of the drug substance dissolves in 15 minutes. The impurity profiles of test and innovator product are also comparable.

Manufacturing process
The manufacturing consists of several mixing steps. The final mixture is tableted with an appropriate press. Validation data for the manufacturing process have been included for one manufacturing site and a protocol has been provided for the other manufacturing site. Process validation data on the product have been presented for three pilot scaled batches of 150 and 300 mg and three production scaled batches of 75 mg. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, uniformity of mass, average weight, dissolution, loss on drying, microbial quality and uniformity of dosage units. The release and shelf life requirements are identical, except for total impurities. Disintegration is performed as in process control. The analytical methods have been adequately described and validated. Batch analytical data from both production sites have been provided on two or three batches demonstrating compliance with the release specification.

Stability tests on the finished product
For one manufacturing site, stability data on the product have been provided on three batches of each strength stored at 25°C/60% RH (18 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months).
For the other manufacturing site, stability data on the product have been provided on two batches of the 75 and 300 mg tablets stored at 25°C/60% RH (9 months), 30°/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PVC-PVdC/Aluminium blisters.
Under all conditions a slight decrease in assay and a slight increase in impurities are observed. Based on the results, a shelf-life of 36 months is justified.
Investigation revealed that the polymorphic form of the drug substance does not change during storage of the drug product. A photostability study has not been performed, but forced degradation results show an increase in impurities. Therefore the storage condition "store in the original package to protect from light" is justified.

Several commitments have been made with regard to the drug product; these can be found on page 8 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Besides lactose, which is derived from milk for human consumption, there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

These products are generic formulations of Karvea 75 mg, 150 mg and 300 mg tablets, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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

II.3 Clinical aspects

Irbesartan is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Licolin 300 mg tablets is compared with the pharmacokinetic profile of the reference product Karvea 300 mg tablets from the Spanish market. The Spanish reference product is acceptable, as Karvea is registered through the centralised procedure EU/1/97/049/001-039.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, open-label, crossover bioequivalence study was carried out under fasted conditions in 28 healthy subjects (14 male/14 female), aged 18-40 years. Each subject received a single dose (300 mg) of one of the 2 irbesartan formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at baseline and at 20', 40', 1h, 1h 20', 1h 40', 2h', 2h 20', 2h 40', 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h and 96h after administration of the products.

Analytical/Statistical methods
A validated technique based on high resolution liquid chromatography coupled to a fluorescence spectroscope (HPLC-FLR), following laboratory good practice, was used to quantify irbesartan in blood plasma. The bioequivalence assessment was done using a parametric approximation for AUC and C_{max} after log-transformation. Parametric pharmacokinetic parameters were analyzed using WinNONLIN. The 90% confidence intervals for the difference between the drug formulations were calculated for the parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$). The pharmacokinetic variables were adequately measured and analysed with suitable statistical methods.

Results
All 28 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of irbesartan under fasted conditions.

Treatment N=28	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	16888 ± 4284	17691 ± 4327	2957 ± 705	-	-
Reference	18080 ± 4619	19183 ± 4994	3149 ± 744	-	-
***Ratio (90% CI)**	0.929 (0.845 - 1.022)	0.921 (0.841 - 1.009)	0.940 (0.846 - 1.044)	-	-
CV (%)	20	19	20	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion
Taking into account the elimination half-life (1.36 ± 5.6 hours), the 7-day washout period is considered acceptable.
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of irbesartan under fasted conditions, it can be concluded that Licolin 300 mg tablets and Karvea 300 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Irbesartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of irbesartan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths
The 75 mg and 150 mg tablets are dose proportional with the 300 mg tablets. The pharmacokinetics of the active substance are linear in the therapeutic dosage range. The different tablet strengths are manufactured by the same manufacturer and manufacturing process. Moreover, the dissolution profiles are comparable. The results of the bioequivalence study performed with the 300 mg tablets therefore apply to the other strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Irbesartan was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irbesartan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Karvea.The SPC has been adapted to the most recent wordings for AIIRA and use during pregnancy and lactation.

Readability test

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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The test was performed on the Spanish version and all questions were in Spanish.

The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated. Age and gender distribution were sufficient. The educational level varied from secondary school completion to university graduates.

After the first round, the PIL was revised. The second round of testing showed that 100% of the participants were able to locate the section, and 100% were able to answer the questions.

During the procedure, the MAH submitted a revised report on the readability test. Several corrections were made to the test results. The member states questioned whether data was recorded and documented in an appropriate way. Therefore, the MAH performed a third test round in order to confirm that readability requirements are met. The PIL was understood by 100% of the participants and 100% of the questions were correctly answered and located. Therewith the readability test has sufficiently demonstrated that the PIL meets the set requirements.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Licolin 75 mg, 150 mg and 300 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Karvea 75 mg, 150 mg and 300 mg tablets. Karvea is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other irbesartan containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Licolin 75 mg, 150 mg and 300 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 April 2010. Licolin 75 mg, 150 mg and 300 mg tablets were authorised in the Netherlands on 11 October 2010.

No European harmonised birth date for irbesartan has been allocated yet. The innovator's PSUR submission scheme will be followed. The first data lock point is October 2011, and subsequently the first PSUR will cover the period from April 2010 to October 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 19 June 2012.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to validate the analytical methods for determination of assay and impurities with regard to robustness in line with Guidance ICH Q2.
- The MAH committed to include a dissolution requirement at shelf life in the specification when following results are available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached