COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Eslibon 200 mg, 400 mg, 600 mg and 800 mg tablets

(eslicarbazepine acetate)

NL/H/4090/001-004/DC

Date: 4 December 2018

This module reflects the scientific discussion for the approval of Eslibon 200 mg, 400 mg, 600 mg and 800 mg tablets. The procedure was finalised at 19 August 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Eslibon 200 mg, 400 mg, 600 mg and 800 mg tablets, from G.L. Pharma GmbH.

The product is indicated as:

- monotherapy in the treatment of partial-onset seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy;
- adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalisation.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zebinix 200 mg, 400 mg, 600 mg and 800 mg tablets which has been registered in the EEA by BIAL - Portela & C, S.A since 21 April 2009 via a centralised procedure (EU/1/09/514).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Czech Republic, Germany and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Eslibon is a white to off-white, oblong, biconvex tablet with a break score on both sides. All tablets can be divided into equal doses. Each tablet contains 200 mg, 400 mg, 600 mg or 800 mg of eslicarbazepine acetate.

The tablets are packed in transparent or opaque PVC/Alu blisters.

The excipients are: croscarmellose sodium, povidone K30 and magnesium stearate.

All tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is eslicarbazepine acetate, an established active substance, not described in the European Pharmacopoeia (Ph.Eur.). Eslicarbazepine acetate is a white or almost white powder. It is practically insoluble in water, sparingly soluble in methanol, slightly soluble in isopropyl alcohol and freely soluble in dimethylsulphoxide and dichloromethane. It is not hygroscopic. Eslicarbazepine acetate has one chiral centre and is synthesised as the S-enantiomer.

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 manufacturing process has been described in sufficient detail and is as per current ASMF. Overall, the process is acceptable.

Quality control of drug substance

The specification consists of the tests for description, identification, purity, related substances, R-isomer, residual solvents (per drug substance manufacturer), assay and microbiological examination. The method of identification is an in-house method. Batch analysis data showing compliance to the specification are provided for two batches. Validation of the analytical procedures has been sufficiently performed.

Stability of drug substance

For the stability of the drug substance reference is made to the ASMF. The proposed re-test periods range from 24-36 months based on long-term stability data of 12-24 months and accelerated stability data of 6 month. The re-test periods can be granted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained.

A bioequivalence study with reference Zebinix 800 mg and applied product Eslicarbazepine acetate 800 mg was conducted to demonstrate similarity *in-vivo*. Biowaivers of strength are requested for the other strengths. Comparative dissolution testing at 3 pHs has been successfully studied. This method shows discriminatory power, only when a time point of 45 min is adopted for QC testing. Overall, the pharmaceutical development can be accepted.

Manufacturing process

The manufacturing process consists of four steps: the preparation of the granulate, the preparation of the tabletting blend and subsequently the preparation of the tablets. The final step is the packaging process. The process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients are in compliance with the Ph. Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, assay, purity, average mass, uniformity of dosage units, dissolution and microbiological limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of the 200 mg strength and four batches of the 400 mg, 600 mg and 800 mg strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for at least three batches of each strength stored at 25°C/60% RH (up to 24 months), 30°C/65% RH (up to 24 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. No out of specification results are obtained. The product is not sensitive to light degradation. On the basis of the data submitted, a shelf life was granted for 24 months.

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

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Eslibon has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Eslibon is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zebinix which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Eslicarbazepine acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Eslibon 200 mg, 400 mg, 600 mg and 800 mg tablets (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product 200 mg, 400 mg, 600 mg and 800 mg tablets (BIAL - Portela & C, S.A., Portugal).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The following prerequisites for requesting a biowaiver for the 200 mg, 400 mg and 600 mg strengths based on the bioequivalence study with the highest strength of 800 mg are met:

- the strengths have been manufactured by the same manufacturing process
- the compositions are qualitatively similar and quantitatively dose proportional
- plasma pharmacokinetics of eslicarbazepine can be considered dose linear in the dose range of 200-800 mg.

Furthermore the MAH has demonstrated similarity of in vitro dissolution at the pH conditions 1.2, 4.5 and 6.8 between the additional lower strengths and the strength used for bioequivalence testing (of the test product). For pH conditions 4.5 and 6.8, this was achieved by comparing same doses using multiple units of the test product, which is acceptable.
Therefore, a biowaiver can be granted for the 200 mg, 400 mg and 600 mg strengths of Esbilon tablets.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 25 healthy male subjects, aged 20-49 years. Each subject received a single dose (800 mg) of one of the 2 eslicarbazepine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 9.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject discontinued the study early. A total of 24 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 licarbazepine under fasted conditions.

Treatment N=24	**AUC_{0-t}** (µg.h/ml)	**$AUC_{0-\infty}$** (µg.h/ml)	**C_{max}** (µg/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	265 ± 61	269 ± 61	13.9 ± 2.4	2.3 0.7 – 6.0	10.3 ± 1.7

Reference	260 ± 54	264 ± 54	13.0 ± 2.4	2.8 1.0 – 5.0	10.1 ± 1.7
***Ratio** **(90% CI)**	1.02 0.99 - 1.04	1.02 0.99 - 1.04	1.07 1.03 - 1.12	--	--
$AUC_{0-\infty}$ 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 on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Eslibon is considered bioequivalent with Zebinix.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Eslibon.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hyponatremia • Cutaneous adverse reactions
Important potential risks	• Thyroid function changes • INR and aPTT increase • Cardiovascular/cerebrovascular ischemia • Potential for suicidality as anti-epileptic drug • Bone disorders
Missing information	• Exposure during pregnancy • Pediatric population (<2 years of age) • Elderly population • Long term effects on brain development, learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zebinix. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The company has provided the following justification for not carrying out user testing:

- The wording of the package leaflet is taken from the originators leaflet (Zebinix 200 mg) as far as possible.
- The identified differences do not affect the usability of the leaflet.
- The layout of the package leaflet will be designed according to the well established corporate layout of the MAH, which has been tested and proven patient friendly.

The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Eslibon 200 mg, 400 mg, 600 mg and 800 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Zebinix 200 mg, 400 mg, 600 mg and 800 mg tablets. Zebinix 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 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 Eslibon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 August 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse