IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Eslicarbazepine acetate Mylan 800 mg Tablets
Eslicarbazepine acetate
PA0577/231/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Eslicarbazepine Acetate Mylan, from McDermott Laboratories Ltd. t/a Gerard Laboratories on 20th March 2020 for 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.

With Ireland as the Reference Member State, a marketing authorisation is applied for in Denmark, France, Italy, Poland, Portugal, Slovenia, and the UK. This decentralised application is submitted as a generic application according to Article 10(1) of Directive 2001/83/EC.

State the prescription status of the products or if there are any other prescription restrictions
In case of line extensions (new indications, pharmaceutical forms) this section can be amended as appropriate.
State, if relevant whether scientific advice was given to the applicant.
Mention EU referral if relevant.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Eslicarbazepine Acetate Mylan 800 mg Tablets
Name(s) of the active substance(s) (INN)	Eslicarbazepine Acetate
Pharmacotherapeutic classification (ATC code)	N03AF Carboxamide derivatives N03AF04 eslicarbazepine
Pharmaceutical form and strength(s)	
Marketing Authorisation Number(s) in Ireland (PA)	PA0577/231/001
Marketing Authorisation Holder	McDermott Laboratories Ltd. t/a Gerard Laboratories
MRP/DCP No.	IE/H/563/001/DC
Reference Member State	IE
Concerned Member States	FR PT IT UK DK PL SI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Eslicarbazepine acetate Mylan 800mg Tablets.

II.2 Drug substance

The active substance is eslicarbazepine acetate, an established active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Eslicarbazepine acetate Mylan 800mg tablets contain 800 mg eslicarbazepine acetate.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Eslicarbazepine acetate Mylan 800mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Zebinix 800 mg Tablets on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of eslicarbazepine acetate are well known. As eslicarbazepine acetate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is acceptable for this type of application.

III.5 Ecotoxicity/environmental risk assessment

Since Eslicarbazepine Acetate Mylan 800 mg Tablets 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.6 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As eslicarbazepine acetate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zebinix 800 mg Tablets marketed by MAH BIAL - Portela & Ca, SA.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Eslicarbazepine acetate Mylan 800 mg is compared with the pharmacokinetic profile of the reference product Zebinix 800 mg Tablets

A two-treatment, two-period, two-sequence, single-dose, crossover study comparing the test and reference product under fasting conditions in healthy, adult, male subjects was carried out. Eslicarbazepine acetate Mylan 800 mg, was compared to the reference product Zebinix 800 mg Tablets. Based on the pharmacokinetic parameters of active substance the reference tablet Zebinix 800 mg Tablets marketed by BIAL - Portela & Ca, SA and test tablet Zebinix 800 mg Tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the study conducted.

IV.2 Pharmacokinetics

Eslicarbazepine acetate is extensively converted to eslicarbazepine. Plasma levels of eslicarbazepine acetate usually remain below the limit of quantification, following oral administration. Eslicarbazepine Cmax is attained at 2 to 3 hours post-dose (tmax). Bioavailability may be assumed as high because the amount of metabolites recovered in urine corresponded to more than 90% of an eslicarbazepine acetate dose.
The pharmacokinetics of eslicarbazepine acetate is linear and dose-proportional in the range 400-1,200 mg both in healthy subjects and patients.

Eslicarbazepine acetate is rapidly and extensively biotransformed to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism. The steady state plasma concentrations are attained after 4 to 5 days of once daily dosing, consistent with an effective half-life in the order of 20-24 hours. In studies in healthy subjects and epileptic adult patients, the apparent half-life of eslicarbazepine was 10-20 hours and 13-20 hours, respectively. Minor metabolites in plasma are Rlicarbazepine and oxcarbazepine, which were shown to be active, and the glucuronic acid conjugates of eslicarbazepine acetate, eslicarbazepine, R-licarbazepine and oxcarbazepine.

IV.3 Pharmacodynamics

The precise mechanisms of action of eslicarbazepine acetate are unknown. However, in vitro electrophysiological studies indicate that both eslicarbazepine acetate and its metabolites stabilise the inactivated state of voltage-gated sodium channels, precluding their return to the activated state and thereby preventing repetitive neuronal firing.

Mechanism of action, primary/secondary pharmacology, dose finding, genetic differences in PD response

IV.4 Clinical Efficacy

No clinical efficacy studies were submitted for this generic application.

IV.5 Clinical Safety

No difference between the test and reference product was detected in terms of reported adverse events in the submitted study.

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 eslicarbazepine acetate. Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

Summary of safety concerns	
Important identified risks	Hyponatremia Cutaneous adverse reactions
Important potential risks	Thyroid function changes International Normalised Ratio (INR) and activated Partial Thromboplastin Time (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

Periodic Safety Update Report (PSUR)

• With regard to PSUR submission, the MAH should take the following into account:
• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

The clinical pharmacology of Eslicarbazepine acetate is well established. Based on the submitted bioequivalence study Eslicarbazepine Acetate Mylan 800 mg Tablets are considered bioequivalent with Zebinix 800 mg Tablets. This study is considered sufficient in the context of this application to support the granting of a marketing authorisation for this product for these indications.

V. OVERALL CONCLUSIONS

Eslicarbazepine acetate Mylan 800mg Tablets is a generic form of Zebinix 800 mg Tablets. Zebinix is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Eslicarbazepine Acetate Mylan 800mg tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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

Regarding the location of the Qualified Person for Pharmacovigilance (QPPV) and Pharmacovigilance System Master File (PSMF): This is currently acceptable. However, in the event of the UK exiting the European Union, the location of the QPPV and PSMF will need to be relocated to a Member State within the European Union.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable

VI. REVISION DATE

07.11.2020