CBG MEB

Public Assessment Report

Scientific discussion

Zilibra 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets

(lacosamide)

NL/H/3945/001-004/DC

Date: 16 April 2019

This module reflects the scientific discussion for the approval of Zilibra 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets. The procedure was finalised on 17 October 2017. 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
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
USP-NF	United States Pharmacopoeia National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zilibra 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets from Pharmaceutical Works Polpharma S.A.

The product is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

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 Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets which has been registered in EEA by UCB Pharma SA through centralised procedure EMEA/H/C/000863 since 29 August 2008.

The concerned member state (CMS) involved in this procedure was Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Zilibra is an oval film-coated tablet debossed with 'LAC' on one side:
- 50 mg film-coated tablets are pinkish and debossed with '50' on the other side.
- 100 mg film-coated tablets are dark yellow and debossed with '100' on the other side.
- 150 mg film-coated tablets are salmon and debossed with '150' on the other side.
- 200 mg film-coated tablets are blue and debossed with '200' on the other side.

The product contains as active substance 50 mg, 100 mg, 150 mg or 200 mg of lacosamide.

The film-coated tablets are packed in a clear, colourless PVC/PVDC blister sealed with an aluminium foil.

The excipients are:
Tablet core - microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylcellulose (low substituted), silicified microcrystalline cellulose, crospovidone (type B) and magnesium stearate.
50 mg tablet coating - poly(vinyl alcohol), macrogol, talc, titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172) and indigotine aluminium lake (E132)
100 mg tablet coating - poly (vinyl alcohol), macrogol, talc, titanium dioxide (E171) and yellow iron oxide (E172)
150 mg tablet coating - poly (vinyl alcohol), macrogol, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172)
200 mg - tablet coating - poly (vinyl alcohol), macrogol, talc, titanium dioxide (E171) and indigotine aluminium lake (E132)

The four tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is lacosamide, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). A draft monograph of lacosamide has been published by the EDQM. Lacosamide is a white to off-white crystalline powder. It is freely soluble in dimethylsulfoxide and in ethanol. Polymorphic form-I was chosen for the development of the product.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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

Manufacturer-I

The drug substance is manufactured at one site while an advanced intermediate is manufactured at another site. The synthesis of an advanced intermediate consists of two steps. Further synthesis of the drug substance consists of a one pot reaction. A sufficiently detailed description of the manufacturing process and process controls has been provided. The proposed starting materials are acceptable. The drug substance has been sufficiently characterised.

Manufacturer-II

The drug substance is manufactured at one manufacturing site. The synthesis consists of four stages. A sufficiently detailed description of the manufacturing process and process controls has been provided. The proposed starting materials are considered acceptable. The drug substance has been sufficiently characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two (manufacturer-I) and three (manufacturer-II) batches.

Stability of drug substance

Manufacturer-I

Manufacturer-I has provided stability data of three batches at 25°C/60% RH for up to 60 months and at 40°C/75% RH for up to six months. Based on the data submitted, a retest period could be granted of five years.

Manufacturer-II

Manufacturer-II has provided stability data of six batches at 25°C/60% RH for up to 48 months and at 40°C/75% RH for up to six months. Based on the data submitted, a retest period could be granted of four years.

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 explained. Pharmaceutical development has been adequately performed.

One bioequivalence study has been submitted. The dissolution results with the 200 mg products used in the bioequivalence study show comparable results as both products show dissolution >85% in 15 minutes.
The MAH also performed dissolution studies to support a biowaiver for the additional tablet strengths. The results are regarded as similar without mathematical evaluation as the dissolution is fast for all tablet strengths (>85% in 15 minutes).

Manufacturing process

The tablets are manufactured using wet granulation. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of the proposed minimum commercial batch size of each tablet strength in accordance with

the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients, except for the coating agent Opadry, are tested according to the current version of the pharmacopoeia. The colouring ingredients included in the film-coatings comply with Commission Regulation (EU) No 231/2012. Silicified microcrystalline cellulose is tested in accordance with United States Pharmacopoeia National Formulary (USP-NF). 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, uniformity of dosage units, related substances, assay, dissolution, and microbiological quality. 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 per tablet strength 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 three batches of each strength in accordance with applicable European guidelines testing the stability of the product for six months at 25°C/60% RH and 40°C/75% RH. Tablets were stored in the proposed packages. On basis of the data submitted, a shelf life was granted of 24 months. The MAH has confirmed the photostability of the tablets when stored outside the primary packaging.

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 Zilibra 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 Zilibra 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 Vimpat 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

Lacosamide 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Zilibra 200 mg (Pharmaceutical Works Polpharma S.A., Poland) is compared with the pharmacokinetic profile of the European reference product Vimpat 200 mg.

The choice of the reference product
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
A biowaiver for the additional 50 mg, 100 mg and 150 mg strengths is granted. The tablets are dose proportional and manufactured with the same manufacturing process. As can be read in the SmPC the pharmacokinetics are linear. Dissolution data at a pH 1.2, 4.5 and 6.8 shows comparable dissolution between the 50 mg, 100 mg and 150 mg tablets versus the 200 mg tablet used in the bioequivalence study.

Design
A single-dose, randomised, crossover bioequivalence study was carried out under fasted conditions in 20 healthy male (n=11) and female (n=9) subjects, aged 24-54 years. Each subject received a single dose (200 mg) of one of the two lacosamide formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting conditions applied in the study are adequate.

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
All 20 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=20	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h

Test	118539 ± 23953	123231 ± 26540	6294 ± 1297	0.83 (0.33 – 4.0)	14.3 ± 3.2
Reference	116994 ± 21680	121576 ± 23656	6153 ± 1376	0.92 (0.33 – 3.0)	14.4 ± 2.8
***Ratio (90% CI)**	1.01 (0.99-1.03)	--	1.03 (0.99-1.07)	--	--
CV (%)	3.5	--	7.5	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Zilibra is considered bioequivalent with Vimpat.

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 Zilibra.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Cardiac adverse events that may be potentially associated with PR interval prolongation and sodium channel modulation • Suicidality • Dizziness
Important potential risks	• Potential for hepatotoxicity • Potential for worsening of seizures • Potential for abuse as a central nervous system (CNS)-active product • Potential for off-label use of a loading dose in acute conditions such as status epilepticus
Missing information	• Pregnant or lactating women • Paediatric patients

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 Vimpat. 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 package leaflet has (PL) 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, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zilibra 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Vimpat 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets. Vimpat 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 Zilibra with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 October 2017.

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