CBG MEB

Public Assessment Report

Scientific discussion

Lacosamide STADA 50 mg, 100 mg, 150 mg and 200 mg, film-coated tablets

(lacosamide)

NL/H/3962/001-004/DC

Date: 27 February 2018

This module reflects the scientific discussion for the approval of Lacosamide STADA 50 mg, 100 mg, 150 mg and 200 mg, film-coated tablets. The procedure was finalised on 21 December 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
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 Lacosamide STADA 50 mg, 100 mg, 150 mg and 200 mg, film-coated tablets from Sieger Pharma 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 (EU/1/08/470) which have been registered in the EEA by UCB Pharma S.A. since 29 August 2018.

The concerned member states (CMS) involved in this procedure were Austria, Germany, Denmark, Spain, Italy, Poland, Sweden and Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

- Lacosamide STADA 50 mg are pink, film coated oblong biconvex tablets, embossed with “50” on one side, plain on the other. Each tablet contains 50 mg lacosamide.
- Lacosamide STADA 100 mg are yellow, film coated oblong biconvex tablets, embossed with “100” on one side, plain on the other. Each tablet contains 100 mg lacosamide.
- Lacosamide STADA 150 mg are beige, film coated oblong biconvex tablets, embossed with “150” on one side, plain on the other. Each tablet contains 150 mg lacosamide.
- Lacosamide STADA 200 mg are blue, film coated oblong biconvex tablets, embossed with “200” on one side, plain on the other. Each tablet contains 200 mg lacosamide.

The film-coated tablets are packed in transparent PVC/PVDC blisters sealed with an aluminium foil.

The excipients are:
Tablet core - cellulose microcrystalline (E460), low-substituted hydroxypropylcellulose, crospovidone (E1202), hydroxypropylcellulose (E463), silica colloidal anhydrous and magnesium stearate
Tablet coating - poly(vinyl alcohol) (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E553b), red iron oxide (E172) (only 50 mg and 150 mg strengths), black iron oxide (E172) (only 50 mg, 100 mg and 150 mg strengths) yellow iron oxide (E172) (only 100 mg and 150 mg strengths), indigo carmine aluminium lake (E132)) (only 50 mg, 150 mg and 200 mg strengths)

II.2 Drug Substance

The active substance is lacosamide, an established active substance not yet described in the European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia and Unites Sated pharmacopeia. A draft monograph of lacosamide has been published by the EDQM (PharmEuropa). The substance is an white to off-white/light yellow powder and sparingly soluble in water. The substance has one chiral centre and is administered in the R-form. The undesired S-isomer is controlled via a specification. Lacosamide exists in 4 different crystalline forms and an amorphous form. Polymorphic form-I is consistently produced. The active substance used for this product comes from two different manufacturers.

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

Manufacturer 1 – The final drug substance is manufactured at one manufacturing site while an advanced intermediate is manufactured at other site in one step. Further synthesis of the drug substance consists of a one pot reaction followed by purification. A sufficiently detailed description of the manufacturing process and process controls has been provided. The proposed starting materials are considered acceptable. The drug substance manufactured at this site has been sufficiently characterised.

Manufacturer 2 - 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 manufactured has been sufficiently characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and consists of the following tests: description, solubility, Identification, related substances, enantiomeric purity, specific optical rotation, melting point, loss on drying, sulfated ash, heavy metals, assay and residual solvents, and polymorphic form. A test and appropriate limits for microbiological quality of the drug substance is not included, this is justified. Justification on the omission of a test for particle size is acceptable. For the analytical methods and their validations the reference is made to the corresponding ASMF's, which is considered acceptable. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance

Manufacturer 1 - Stability data on the active substance have been provided for 4 batches, stored at 25°C/65% RH (up to 30 months) and 40°C/75% RH (up to 6 months). The conditions used in the studies are in accordance with applicable European guidelines. Results of the stability studies are all within specifications. The proposed re-test period of 24 months when stored in airtight containers at temperature below 25 °C is acceptable. The storage restrictions are not necessary but no objection will be made as this is a common storage condition.

Manufacturer 2 - Stability data on the active substance have been provided for 6 batches, stored at 25°C/65% RH (up to 48 months) and 40°C/75% RH (up to 6 months). A re-test period of 4 years has been requested by the MAH, which is justified.

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. The development of the dissolution method to be used for routine testing of the test product has been adequately discussed and the dissolution conditions have been justified. To support the application, the MAH has performed one bioequivalence study between Lacosamide STADA 200 mg, film-coated tablets and the innovator product Vimpat 200 mg film-coated tablets. For the other strengths, 50 mg, 100 mg and 150 mg, a biowaiver has been requested. Comparative *in-vitro* dissolution profile data on the test product Lacosamide 50mg, 100mg, 150mg and 200mg film-coated tablets and reference product Vimpat 200 mg film-coated tablets in 0.1N Hydrochloric acid, pH 4.5 buffer and pH 6.8 phosphate has been provided. The batches tested included the bio-batches.

Manufacturing process
The manufacturing process is considered as being a standard process and has been validated according to relevant European guidelines. Process steps include: preparation, mixing, drying, sizing, lubrication, compression, coating and packaging. Process validation data on the product have been presented for multiple batches in accordance with the relevant European guidelines.

Control of excipients
All excipients, except the colouring agents, comply with the Ph.Eur. The individual components of the coating agent comply with their respective Ph.Eur. monograph and the colouring agents meet the requirements of EU regulation no 231/2012. The 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, disintegration, dissolution, uniformity, assay and purity. 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 3 batches of each strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches of each strength stored at 25˚C/60% RH (30 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The photostability study did not show a decrease in the assay compared to the control samples or increase in impurities. On basis of the data submitted, a shelf life was granted of 30 months. No specific storage conditions need to be included.

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 Lacosamide STADA 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 Lacosamide STADA 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 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 Lacosamide STADA 200 mg, film-coated tablets (Sieger Pharma S.A., Greece) is compared with the pharmacokinetic profile of the reference product Vimpat 200 mg film-coated tablets (UCB Pharma S.A., Belgium).

The choice of the reference product in the bioequivalence studies is accepted, as Vimpat has been registered trough a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver for the additional strengths 50 mg, 100 mg and 150 mg has been applied for. The biowaiver can be granted as all of the following criteria for a biowaiver based on the current Guideline on the Investigation of Bioequivalence are met:

- pharmacokinetics are linear over the dose range
- all strengths are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of strengths is quantitatively proportional
- appropriate in vitro dissolution data are available at two different buffers (pH 4.5 and pH 6.8) and the QC medium (HCl 0.1N)

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 22-39 years. Each subject received a single dose (200 mg) of one of the 2 lacosamide 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 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.33 ,3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

lacosamide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of lacosamide. 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.

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
Two subjects did not report back for the second period and were considered as drop-outs. Therefore, a total of 22 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 lacosamide under fasted conditions.

Treatment N=22	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	117849 ± 15522	122284 ± 16349	81267± 1910	0.75 (0.25 – 2.33)
Reference	120042 ± 15173	125142 ± 15806	7883 ± 1853	0.75 (0.50 – 2.67)
***Ratio (90% CI)**	0.98 (0.95 – 1.01)	--	1.03 (0.95 – 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
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 Lacosamide STADA 200 mg, film-coated tablets is considered bioequivalent with Vimpat 200 mg film-coated tablets..

The results of study 16-003 with Lacosamide STADA 200 mg, film-coated tablet can be extrapolated to other strengths 50, 100 and 150 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Lacosamide STADA.

- 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	– Hepatotoxicity – Potential for worsening of seizures – Potential for abuse as an CNS-active product – Potential for off-label use of a loading dose in acute conditions such as status epilepticus
Missing information	– Use in pregnant and lactating women – Use in 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 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lacosamide STADA 50 mg, 100 mg, 150 mg and 200 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Vimpat 50 mg, 100 mg, 150 mg and 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 Lacosamide STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 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