LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lacosamide Medical Valley
(lacosamide)

SE/H/1904/01-05/DC
2018-1164--1168

This module reflects the scientific discussion for the approval of Lacosamide Medical Valley. The procedure was finalised on 2020-03-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Lacosamide Medical Valley, 50 mg, 100 mg, 150 mg, 200 mg film-coated tablet and 10 mg/ml syrup, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medical Valley Invest AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, FI, IS, NL and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Vimpat 50 mg, 100 mg, 150 mg, 200 mg film-coated tablet and 10 mg/ml syrup authorised in the Community since 2008, with UCB Pharma S.A. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetic properties of the active substance
Absorption: Lacosamide has an oral bioavailability of approximately 100 %. Following an oral dose of lacosamide maximal plasma concentrations occur at approximately 0.5 to 4 hours.

The pharmacokinetics of lacosamide is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The plasma concentration increases proportionally with dose after oral administration (100-800 mg).

Elimination: Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. The terminal half-life is 13 hours.

Tablets
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, in-vitro dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

The applicant claims the biowaiver justified as:

- Lacosamide has been proven to exhibit high solubility and complete absorption
- The drug product has very rapid in vitro dissolution behaviour, similar to the reference product
- There are some small differences in excipients, but none of them is known to influence bioavailability
- Lacosamide is not considered a narrow therapeutic index drug

Syrup
According to the Guideline on the investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1), bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution. However, if the excipients may affect gastrointestinal transit, absorption, solubility or stability, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data.

The applicant claims the biowaiver for oral solution is justified as:

- The active substance is completely in solution in the product
- The highest strength is soluble in 250 ml of aqueous media in the pH range 1 to 7.5
- The active substance is considered highly permeable having linear and complete absorption, about 95% after oral administration
- The qualitative composition of test and reference product are considered similar regarding excipients that may influence absorption - equal amounts of sorbitol in both compositions

Discussion and overall conclusion
Tablets: It can be concluded that the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I). None of the excipients included in the drug product are known to influence bioavailability. The difference in excipients is acceptable for a BCS class I-biowaiver. Lacosamide does not have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with lacosamide. The quality criteria for biowaiver (solubility and dissolution) have also been fulfilled. In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

Syrup: The qualitative composition of test and reference product is similar. The applicant has adequately discussed the quantitative composition of excipients that might affect bioavailability. Particularly, the amount of sorbitol is the same in test and reference product. The justification for a biowaiver for oral solution is acceptable since it fulfils the criteria for biowaiver.

Thus, the absence of bioequivalence studies is acceptable for tablets and syrup.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted an updated 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 Medical Valley.

Safety specification

Summary of safety concerns	
Important identified risks	• Cardiac AEs that may be potentially associated with PR interval prolongation and sodium channel modulation • Suicidality • Dizziness
Important potential risks	• Potential for hepatotoxicity • Potential for worsening seizures • Potential for abuse as a CNS-active substance • Potential for off-label use of a loading dose in acute conditions such as status epilepticus
Missing information	• Pregnant or lactating women • Impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 7th March 2019 is considered acceptable. The submitted Risk Management Plan, version 1.1 signed is in line with the RMP (version 12.2) agreed for the reference product Vimpat in variation EMEA/H/C/000863/II/0065/G.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vimpat EMEA/H/C/000863 (17/09/2008). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lacosamide Medical Valley, is found adequate. There are no objections to approval of Lacosamide Medical Valley from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Lacosamide Medical Valley, 50 mg, 100 mg, 150 mg, 200 mg film-coated tablet and 10 mg/ml syrup was positively finalised on 2020-03-05.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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