LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Trelema
(lacosamide)

SE/H/1648/01-07/DC

This module reflects the scientific discussion for the approval of Trelema. The procedure was finalised on 2018-03-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Trelema

- Film-coated tablet 50 mg, 100 mg, 150 mg, 200 mg
- Solution for infusion, 10 mg/ml
- Syrup, 10 mg/ml

is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, G.L. Pharma GmbH applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BG, CZ, HU, PL, SK, UK as concerned member states (CMS). The application was withdrawn in ES and NL during the first step of the procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Vimpat, authorised in Union since 2008, with UCB Pharma GmbH 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

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. The plasma concentration increases proportionally with dose after oral (100-800 mg) and i.v. (50-300 mg) administration. Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. The terminal half-life is 13 hours.

No bioequivalence studies have been submitted. The applicant has applied for biowaivers as indicated below.

Tablets
The applicant applies for a BCS class I based biowaiver. From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same. A BCS-based biowaiver is only possible for substances that are not considered to have a narrow therapeutic index.

The applicant states that lacosamide is a modified amino-acid with a fast and complete absorption. The bioavailability after oral administration approaches 100%. It is agreed that it can be concluded that the extent of absorption is above 85% and thus that lacosamide can be classified as a BCS class I substance from a pharmacokinetic perspective.

The applied product and the reference product have the same qualitative composition and similar quantitative composition. None of the excipients used are known to influence bioavailability. Thus, the difference in excipients is acceptable for a BCS class I-biowaiver. The quality criteria for biowaiver (solubility and dissolution) have also been fulfilled.

It can be concluded that lacosamide does not have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with lacosamide.

In conclusion, the BCS based biowaiver is acceptable.

Syrup
The applicant claims that a bioequivalence study is not necessary since the product is an aqueous oral solution. According to the Guideline on the investigation of Bioequivalence (CHMP/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 qualitative composition of test and reference product is similar. The applicant has adequately discussed the quantitative composition of excipients that might affect bioavailability. In particular, the amount of sorbitol is the same in test and reference product. Thus, a waiver from bioequivalence studies is acceptable.

Solution for infusion
For the solution for infusion, the applicant claims that a bioequivalence study is not necessary since the product is an aqueous parenteral solution. The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. None of the excipients are known to interact with the drug substance. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1).

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

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 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 Trelema.

Safety specification
Summary table of safety concerns as approved proposed by the Applicant in RMP

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**

Summary of safety concerns	
Missing information	- **Pregnant or lactating women** - **Pediatric patients**

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant. The routine pharmacovigilance activities including guided questionnaire for cardiac AEs that may be potentially associated with PR interval is described in the RMP in agreement with the originators RMP (Annex 7).

The Applicant added statement that HCPs are encouraged to register and report pregnancy cases of women with epilepsy to EURAP to support the collection of additional data on pregnancy under therapy with lacosamide in EURAP for comparison of different anti-epileptics regarding teratogenicity.

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

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP
The MAA should commit that the summary of safety concerns and all corresponding sections of the RMP, including risk minimization measures and pharmacovigilance measures are aligned with the RMP for the originator.

Summary of the RMP
The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the centrally approved reference product Vimpat, regarding content and to Oxycodon HCl 5/10/20/40/80 mg prolonged-release tablets, DE/H/2182/001-005/DC, regarding layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products, Trelema

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is found adequate. There are no objections to approval of Trelema, 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 Trelema

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- Solution for infusion, 10 mg/ml
- Syrup, 10 mg/ml

was positively finalised on 2018-03-08.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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