COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(lacosamide)

NL/H/4992/001-004/DC

Date: 10 February 2021

This module reflects the scientific discussion for the approval of Lacosamide Amarox 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets. The procedure was finalised at 21 December 2020. 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 Amarox 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets, from Amarox Pharma B.V.

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 2008.

The concerned member states (CMS) involved in this procedure were Germany, Spain and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

- Lacosamide Amarox 50 mg is a pink coloured, oval shaped, biconvex, film-coated tablet, debossed with 'J' on one side and '12' on the other side. Each tablet contains 50 mg lacosamide.
- Lacosamide Amarox 100 mg is a yellow coloured, oval shaped, biconvex, film-coated tablet, debossed with 'J' on one side and '13' on the other side. Each tablet contains 100 mg lacosamide.
- Lacosamide Amarox 150 mg is a salmon coloured, oval shaped, biconvex, film-coated tablet, debossed with 'J' on one side and '14' on the other side. Each tablet contains 150 mg lacosamide.
- Lacosamide Amarox 200 mg is a blue coloured, oval shaped, biconvex, film-coated tablet debossed with 'J' on one side and '15' on the other side. Each tablet contains 200 mg lacosamide.

The film-coated tablets are packed in Clear PVC/PVDC-aluminium blister packs.

The excipients are:
Tablet core - microcrystalline cellulose, (E460), hydroxypropylcellulose (E463), crospovidone (E1202), colloidal anhydrous silica, magnesium stearate
Tablet coat -

- 50 mg strength: polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol (E1521), red iron oxide (E172), lecithin (E322), indigo carmine aluminium lake (E132) and black iron oxide (E172)
- 100 mg strength: polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol (E1521), yellow iron oxide (E172) and lecithin (E322)
- 150 mg strength: polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol (E1521), lecithin (E322), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172)
- 200 mg strength: polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171), macrogol (E1521), indigo carmine aluminium lake (E132) and lecithin (E322)
- Clear coat (all strengths): hypromellose (E464) and macrogol (E1521)

II.2 Drug Substance

The active substance is lacosamide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Lacosamide is a white or almost white or light yellow powder. It is sparingly soluble in water, freely soluble in methanol and practically insoluble in n-Heptane. The polymorphic form-I is consistently produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP, with additionally tests for the residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for several batches.

Stability of drug substance
No re-test period is indicated on the CEP. The re-test period of 60 months without special storage conditions is supported by stability data provided by the MAH.

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. Data have been provided demonstrating that the polymorphic form-I remains after manufacture and during storage.

The dissolution studies show that active substance dissolves fast and complete from the film-coated tablets regardless of dissolution medium used. The dissolution results with the products used in the bioequivalence study (200 mg proposed product vs. innovator product) show comparable results as both product show dissolution > 85% in 15 minutes. The MAH also performed dissolution studies to support biowaiver for the additional tablet strengths. The results can be regarded as similar without mathematical evaluation as the dissolution is fast for all tablet strengths (> 85% in 15 minutes). Overall, the pharmaceutical development has been adequately described.

Manufacturing process

The film-coated tablets are manufactured using wet granulation. The manufacturing process has been adequality described and validated according to relevant European guidelines. Process validation data on the product have been presented for several commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients

All excipients are corresponding with their Ph. Eur. monographs. 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, average weight, uniformity of dosage units, water content, 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 twelve batches 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 per strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended packaging. The photostability study showed that the product is not light sensitive. On basis of the data submitted, a shelf life was granted of 2 years, without any special storage conditions.

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 Amarox 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 Amarox 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 Amarox 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets (Amarox Pharma B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets (UCB Pharma S.A., Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product

Biowaiver

A biowaiver to 50, 100 and 150 mg strengths is acceptable based on the following:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the composition of the strengths are quantitatively proportional
d) similarity in in vitro dissolution profiles, i.e. all additional strengths show very rapid dissolution, >85% in 15 min, at all three pH levels of 1.2, 4.5 and 6.8 using paddle apparatus at 50 rpm.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 34 healthy male subjects, aged 32 ± 6 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. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.25, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after administration of the products.

A single dose study under fasting conditions with the highest, 200 mg, strength is considered sufficient to support an application for an immediate-release product with several strengths. The proposed products can be taken with and without food. Hence, a study in the fasting condition is agreed as this more sensitive to detect differences between the test and reference product in accordance to the Guideline on the Investigation of 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

One subject was withdrawn from the study due to an adverse event. Therefore, 33 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=33	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	107349 ± 14772	113586 ± 17375	6775 ± 1439	0.50 (0.33 - 3.00)	16.75 ± 2.80
Reference	106781 ± 14686	112637 ± 17054	7427 ± 2052	0.50 (0.17 – 3.67)	17.07 ± 2.58
***Ratio (90% CI)**	1.00 (0.98 – 1.03)	1.01 (0.99 – 1.03)	0.93 (0.86 – 1.00)	--	--
CV (%)	18.0	5.0	4.8	--	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Lacosamide Amarox 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 Lacosamide Amarox.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation • Suicidality • Dizziness

Important potential risks	• Potential for hepatotoxicity • Potential for worsening of seizures • Potential for abuse as a 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 • Impact on long-term growth, long-term neurodevelopment, and on puberty in paediatric population aged 4 to < 16 years

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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets (EMA/504905/2017) with respect to content and Levetiracetam Hetero 750 mg film-coated tablets (PT/H/515/01-04/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lacosamide Amarox 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 Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 2020.

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