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Public Assessment Report

Name of the Product:

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

(lacosamide)

Procedure number: HU/H/0663/001-004/DC

Marketing authorisation holder: Alkaloid-INT d.o.o.

Date: 11. 03. 2021.

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets. The holder of the marketing authorisation is Alkaloid-INT d.o.o.

The active substance is lacosamide.

- Losmorid 50 mg film-coated tablets: each film-coated tablet contains 50 mg of lacosamide

- Losmorid 100 mg film-coated tablets: each film-coated tablet contains 100 mg of lacosamide

- Losmorid 150 mg film-coated tablets: each film-coated tablet contains 150 mg of lacosamide

- Losmorid 200 mg film-coated tablets: each film-coated tablet contains 200 mg of lacosamide

The other ingredients are:

– tablet core: microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, hydroxypropylcellulose, silica colloidal anhydrous, magnesium stearate

– film-coating: poly(vinyl alcohol), macrogol, titanium dioxide (E171), talc

The appearance of the tablets is:
- The 50 mg film-coated tablets are pink, film-coated oblong biconvex tablets, embossed with ‘50’ on one side, plain on the other with 10.3 mm length and 4.8 mm width approximately.
- The 100 mg film-coated tablets are yellow, film-coated oblong biconvex tablets, embossed with ‘100’ on one side, plain on the other with 13.1 mm length and 6.1 mm width approximately.
- The 150 mg film-coated tablets are beige, film-coated oblong biconvex tablets, embossed with ‘150’ on one side, plain on the other with 15.2 mm length and 7.1 mm width approximately.
- The 200 mg film-coated tablets are blue, film-coated oblong biconvex tablets, embossed with ‘200’ on one side, plain on the other with 16.6 mm length and 7.7 mm width approximately.

The film-coated tablets are available in packs in blisters.

Losmorid is used in adults, adolescents and children aged 4 years and older.

It is used to treat a certain type of epilepsy characterised by the occurrence of partial-onset seizure with or without secondary generalisation.

In this type of epilepsy, fits first affect only one side of your brain. However, these may then spread to larger areas on both sides of the brain.

Losmorid may be used on its own or with other antiepileptic medicines.

What patients need to know before using Losmorid

Patients must not take Losmorid if they

- are allergic to lacosamide or any of the other ingredients of this medicine (listed above). If patients are not sure whether they are allergic, they need to discuss with their doctor.

- have a certain type of heart beat problem called second- or third-degree AV block.

Warnings and precautions

Patients must talk to their doctor before taking Losmorid if they

- have thoughts of harming or killing themself. A small number of people being treated with antiepileptic medicinal products such as lacosamide have had thoughts of harming or killing themselves. In case of having any of these thoughts at any time, patients must tell their doctor straight away.
- have a heart problem that affects the beat of the heart and they often have a particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation and atrial flutter);
- have severe heart disease such as heart failure or have had a heart attack;
- are often dizzy or fall over. Losmorid may make patients dizzy - this could increase the risk of accidental injury or a fall. This means that they should take care until they are used to the effects of this medicine.

If any of the above apply to the patients (or they are not sure), they must talk to their doctor or pharmacist before taking Losmorid.

In the event of taking Losmorid and experiencing symptoms of abnormal heartbeat (such as slow, rapid or irregular heartbeat, palpitations, shortness of breath, feeling lightheaded, fainting), medical advice should be seeked immediately.

Children under 4 years

Losmorid is not recommended for children aged under 4 years. This is because we do not yet know whether it will work and whether it is safe for children in this age group.

Other medicines and Losmorid

Those who are taking, have recently taken or might take any other medicines must consult their doctor.
Consulting the doctor or pharmacist is especially important if patients are taking any of the following medicines that affect their heart - this is because Losmorid can also affect their heart:

- medicines to treat heart problems;
- medicines which can increase the "PR interval" on a scan of the heart (ECG or electrocardiogram) such as medicines for epilepsy or pain called carbamazepine, lamotrigine or pregabalin;
- medicines used to treat certain types of irregular heartbeat or heart failure.

In case of taking any of the following medicines, the doctor or pharmacist should be contacted as well. This is because they may increase or decrease the effect of Losmorid on patients' body:

- medicines for fungal infections called fluconazole, itraconazole or ketoconazole;
- a medicine for HIV called ritonavir;
- medicines used to treat bacterial infections called clarithromycin or rifampicin;
- a herbal medicine used to treat mild anxiety and depression called St. John's wort.

If any of the above apply to the patients (or they are not sure), they must talk to their doctor or pharmacist before taking Losmorid.

Losmorid with alcohol

As a safety precaution taking Losmorid with alcohol is not allowed.

Pregnancy and breast-feeding

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, doctor or pharmacist should be asked for advice before taking this medicine.

It is not recommended to take Losmorid if patients are pregnant or breast-feeding, as the effects of lacosamide on pregnancy and the unborn baby or the new-born child are not known. Also, it is not known whether lacosamide passes into breast milk. In case of getting pregnant or are planning to become pregnant, patients must seek advice immediately from their doctor. They will help them decide if they should take Losmorid or not.

It is not allowed to stop the treatment without talking to the doctor first as this could increase patients' fits (seizures). A worsening of the disease can also harm the baby.

Driving and using machines

It is not allowed to drive, cycle or use any tools or machines until patients know how this medicine affects them. This is because Losmorid may make them feel dizzy or cause blurred vision.

How to use Losmorid

This medicine must always be taken exactly as the doctor or pharmacist has told patients. If patients are not sure the doctor or pharmacist should be checked with.

Patients need to
- take Losmorid twice each day - once in the morning and once in the evening.
- try to take it at about the same time each day.
- swallow the Losmorid tablet with a glass of water.
- take Losmorid with or without food.

Patients will usually start by taking a low dose each day and their doctor will slowly increase this over a number of weeks. When they reach the dose that works for them, this is called the "maintenance dose", they then take the same amount each day. Losmorid is used as a long term treatment. It is necessary to continue to take Losmorid until the doctor tells patients to stop.

How much Losmorid to use

Listed below are the normal recommended doses of Losmorid for different age groups and weights. The doctor may prescribe a different dose in case of any problems with the kidneys or with the liver.

Adolescents and children weighing 50 kg or more and adults
Taking Losmorid monotherapy
The usual starting dose of Losmorid is 50 mg twice a day.
The doctor may also prescribe a starting dose of 100 mg of Losmorid twice a day.

The doctor may increase the twice daily dose every week by 50 mg. This will be until they reach a maintenance dose between 100 mg and 300 mg twice a day.

Taking Losmorid with other antiepileptic medicines
The usual starting dose of Losmorid is 50 mg twice a day.

The doctor may increase the twice daily dose every week by 50 mg. This will be until they reach a maintenance dose between 100 mg and 200 mg twice a day.

In case of a weight of 50 kg or more, the doctor may decide to start Losmorid treatment with a single "loading" dose of 200 mg. They would then start their ongoing maintenance dose 12 hours later.

Children and adolescent weighing less than 50 kg
The dose depends on their body weight. For dosages below 50 mg lacosamide syrup may be available. They usually start treatment with the syrup and only change to tablets if they are able to take tablets and get the correct dose with the different tablet strengths. The doctor will prescribe the formulation that is best suited to them.

What to do if more Losmorid was taken that it should have been?

In the event of an accidental overdose the doctor or the nearest accident and emergency department must be contacted. Trying to drive is not allowed.

Patients may experience:
- dizziness;
- feeling sick (nausea) or being sick (vomiting);
- fits (seizures), heartbeat problems such a slow, fast or irregular heartbeat, coma or a fall in blood pressure with rapid heartbeat and sweating.

What to do if taking Losmorid was forgotten?

- If patients have missed a dose within the first 6 hours of the scheduled dose, they should take it as soon as they remember.
- If patients have missed a dose beyond the first 6 hours of the scheduled dose, they should not take the missed tablet anymore. Instead they should take Losmorid at the next time that they would normally take it.
- No double dose to make up for a forgotten dose must be taken.

May patients stop taking Losmorid?

Taking Losmorid must not be stopped without talking to the doctor, as epilepsy may come back again or become worse. If the doctor decides to stop the treatment with Losmorid, they will tell patients how to decrease the dose step by step.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Nervous system side effects such as dizziness may be higher after a single “loading” dose.

Experiencing any of the following, the doctor or pharmacist must be contacted:

Very common: may affect more than 1 in 10 people
- headache;
- feeling dizzy or sick (nausea);
- double vision (diplopia).

Common: may affect up to 1 in 10 people
- problems in keeping your balance, shaking (tremor), tingling (paresthesia) or muscle spasms, falling easily and getting bruises;
- troubles with memory, thinking or finding words, confusion;
- rapid and uncontrollable movements of the eyes (nystagmus), blurred vision;

- a spinning sensation (vertigo), feeling drunk;
- being sick (vomiting), dry mouth, constipation, indigestion, excessive gas in the stomach or bowel, diarrhoea;
- decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention;
- noise in the ear such as buzzing, ringing or whistling;
- irritability, trouble sleeping, depression;
- sleepiness, tiredness or weakness (asthenia);
- itching, rash.

Uncommon: may affect up to 1 in 100 people
- slow heart rate, palpitations, irregular pulse or other changes in the electrical activity of your heart (conduction disorder);
- exaggerated feeling of wellbeing, seeing and/or hearing things which are not there;
- allergic reaction to medicine intake, hives;
- blood tests may show abnormal liver function, liver injury;
- thoughts of harming or killing yourself or attempting suicide: contacting the doctor is an urgent need;
- feeling angry or agitated;
- abnormal thinking or losing touch with reality;
- serious allergic reaction which causes swelling of the face, throat, hands, feet, ankles, or lower legs;
- fainting;
- difficulties in coordinating your movements or walking.

Not known: frequency cannot be estimated from available data
- abnormal rapid heartbeat (ventricular tachyarrhythmia);
- a sore throat, high temperature and getting more infections than usual. Blood tests may show a severe decrease in a specific class of white blood cells (agranulocytosis);
- a serious skin reaction which may include a high temperature and other flu-like symptoms, a rash on the face, extended rash, swollen glands (enlarged lymph nodes). Blood tests may show increased levels of liver enzymes and a type of white blood cell (eosinophilia);
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens–Johnson syndrome), and a more severe form causing skin peeling in more than 30 % of the body surface (toxic epidermal necrolysis);
- convulsion.

Additional side effects in children

Common: may affect up to 1 in 10 children
- runny nose (nasopharyngitis);
- fever (pyrexia);
- sore throat (pharyngitis);
- eating less than usual.

Uncommon: may affect up to 1 in 100 children
- feeling sleepy or lacking in energy (lethargy).

Not known: frequency cannot be estimated from available data
- changes in behaviour, not acting like themselves.

How to store Losmorid

This medicine does not require any special temperature storage conditions. It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets. The procedure was finalised at 08 December 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, con-cerned member state, CMS: Bulgaria, Croatia and Slovenia) concerned the generic version of lacosamide 50 mg, 100 mg, 150 mg and 200 mg.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC (generic application) and there-fore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product and reference product.

The reference product is Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets by UCB Pharma SA approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets from Alkaloid-INT d.o.o.

Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets are 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 Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

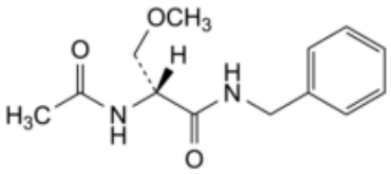
The chemical-pharmaceutical assessment report concerns the application of Losmorid 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The products have been developed by Genepharm S.A.

Reference products are Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets (containing 50 mg, 100 mg, 150 mg and 200 mg lacosamide as active ingredient) which were the products of UCB Pharma SA.

II.2 Drug substance – Lacosamide

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) and Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: lacosamide
Chemical name: (2R)-2-(acetylamino)-N-benzyl-3-methoxypropanamide
Structure:



The active substance is white to light yellow powder, sparingly soluble in water and slightly soluble in acetonitrile and ethanol. It shows polymorphism, the manufacturers consistently produce the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, XRDP, UV spectroscopy and elemental analysis. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data in ASMF the proposed re-test period is acceptable with the proposed storage conditions. Regarding active substance manufacturer with CEP the re-test period and the packaging material have been mentioned on the CEP.

Good Manufacturing Practice (GMP) compliance of the active pharmaceutical ingredient (API) manufacture is demonstrated by the Applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing lacosamide as drug substance in 50 mg, 100 mg, 150 mg and 200 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets, the branded original products of UCB Pharma SA.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

- 50 mg: pink, film coated oblong biconvex tablets, embossed with “50” on one side, plain on the other with 10.3 mm length and 4.8 mm width approximately.
- 100 mg: yellow, film coated oblong biconvex tablets, embossed with “100” on one side, plain on the other with 13.1 mm length and 6.1 mm width approximately.
- 150 mg: beige, film coated oblong biconvex tablets, embossed with “150” on one side, plain on the other with 15.2 mm length and 7.1 mm width approximately.
- 200 mg: blue, film coated oblong biconvex tablets, embossed with “200” on one side, plain on the other with 16.6 mm length and 7.7 mm width approximately.

The excipients used in the finished product are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, hydroxypropylcellulose, colloidal anhydrous silica, magnesium and film-coating (poly(vinyl alcohol), macrogol 3350, titanium dioxide (E171), talc, red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172) and indigo carmine

aluminium lake (E132)). All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is transparent PVC/PVdC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 4 years with no special storage conditions** is approved.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of lacosamide are well known. As lacosamide is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, lacosamide. Overview based on literature review is appropriate.

III.2 Pharmacology

The drug product Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets contains the active substance lacosamide, which is a functionalised amino acid with a chemical structure based on the D-serine moiety. . Lacosamide is believed to exert its anticonvulsant effects by novel mechanisms of action. In the quest to determine the pharmacodynamics properties of lacosamide, the initial studies evaluated whether it shared some of the known mechanisms of action of other antiepileptic drugs (AEDs). Using electrophysiological and radioligand binding techniques, lacosamide had no relevant effect on the known target sites for AEDs. Two potential mechanisms of action for LCM have been proposed. The first is selective enhancement of slow inactivation of voltage-gated sodium channels (VGSCs) and the second is related to the interaction of LCM with the collapsing-response mediator protein-2 protein (CRMP-2).
By increasing the proportion of sodium channels undergoing slow inactivation at any given membrane potential, LCM reduces the pool of neurons available for depolarization, thereby decreasing the probability of seizure occurrence. In conclusion, LCM enhances a mechanism that may decrease the hyperexcitable state in an epileptic focus by enhancing the slow inactivation of VGSCs without affecting physiological fast inactivation.
Preliminary experiments suggest that LCM interacts with the CRMP-2 protein; the relevance of these observations is currently under investigation. Experimental studies further suggested that LCM may exert a modulatory effect on CRMP-2-induced axonal outgrowth of primary hippocampal cells following stimulation with neurotrophic factors. LCM showed no effect on basal axonal growth. By interacting with the CRMP-2, it is postulated that LCM may have symptomatic and/or disease-modifying effects.
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

III.4 Toxicology

Published information on toxicological studies with lacosamide was the basis for the evaluation.
No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmnetal risk assessment (ERA)

An ERA was not submitted with this marketing authorization, based on the fact that this generic product is intended to substitute for other identical products on the market, therefore the approval of the referred product should not result in an increase of the total quantity of lacosamide released into the environment.
Since Losmorid is intended for generic substitution, and there are already other generic formulations of lacosamide on the market – that is, Losmorid is not a new generic medicinal product – it can be presumed that its introduction will not lead to an increased exposure to the environment. With this regard, a formal environmental risk assessment for Losmorid is therefore not deemed necessary.

III.6 Discussion onthe non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of lacosamide are well-known. As Losmorid is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is thus acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Except for showing bioequivalence no new non-clinical pharmacokinetic studies were conducted by the Applicant as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.
The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches Cmax about 0.5 to 4 hours post-dose. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
The metabolism of lacosamide has not been completely characterised. 95% of the dose is excreted in the urine as active substance and metabolites. The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore, an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor. The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabelled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged active substance is approximately 13 hours.

The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3-day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment

The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with end-stage renal disease requiring haemodialysis compared to healthy subjects, whereas C_{max} was unaffected.

Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore, dosage supplementation following haemodialysis is recommended. The exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment

Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUCnorm). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment.

Elderly (over 65 years of age)

In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.

A general dose reduction is not considered to be necessary unless indicated due to reduced renal function.

Paediatric population

The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in one placebo-controlled

randomised study and three open-label studies in 414 children with epilepsy aged 6 months to 17 years. The administered la-cosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, with a maximum of 600 mg/day for children weighing 50 kg or more.
The typical plasma clearance was estimated to be 1.04 L/h, 1.32 L/h and 1.86 L/h for children weighing 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.92 L/h in adults (70 kg body weight).

Bioequivalence

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product and reference product (Study code: 16-003).
The pivotal bioequivalence study was performed in order to support essential similarity between the test product Lacosamide 200 mg film-coated tablets (Genepharm S.A., Greece) and the reference product Vimpat® 200 mg film-coated tablets (UCB Pharma, S.A., Belgium) in healthy male volunteers under fasting conditions according to the bioequivalence guideline in force (*CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010*).

On the basis of results of bioequivalence study coded 16-003 the Lacosamide 200 mg film-coated tablets (manufactured by Genepharm S.A, Greece) (Test) and Vimpat® 200 mg film coated tablets (lacosamide) (manufactured by Aesica Pharmaceuticals GmbH, Germany, MAH: UCB Pharma S.A., Belgium) (Reference) are bioequivalent in healthy adult subjects under fasting conditions.

Bioequivalence study No. 16-003

Main objective: to compare the rate and extent of absorption of the Test- and Reference products administered to healthy volunteers in a single dose under fasting conditions.
Design of this investigation was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence bioequivalence study of lacosamide with a 7-day washout period in healthy male subjects under fasting condition.
Number of subjects: 24 subjects were randomized and dosed in Period 1 of the study, 2 subjects were withdrawn from the study, 22 subjects completed the protocol and were included in pharmacokinetic analysis.
Samples taken per period:
A total of 26 blood samples were taken at per period: pre-dose (0.00) and at 0.25, 0.5, 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 post dose (05 mL each).
Analytical method:
Determination of (R)-Lacosamide in plasma samples was performed using a chiral LC-MS/MS method by extracting samples using liquid-liquid extraction method.
Results of the performed ISR experiment met the acceptance criteria, as 92.8% of the 125 incurred samples were within the acceptance range.
Statistical methods used in the evaluation of BE

- Log-transformation of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} data
- Evaluation of data using a linear mixed-effects model (SAS® version 9.4), with the main effects of *treatment*, *period*, *sequence* and *subjects nested within sequence* in ANOVA
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level)
- Applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon's test)

Bioequivalence criteria:

Test product could be considered bioequivalent to the Reference product, when the ln-transformed Test/Reference LS (least-squares) mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters falled entirely within the acceptance range of 80.00 - 125.00% for (R)-Lacosamide.

GCP aspects:

By the Sponsor's statement the study was conducted in compliance with the requirements of guideline on *Good Clinical Practice, ICH Topic E6* (*CPMP/ICH/135/95*), and *Guideline on the investigation of bioequivalence* (*CPMP/EWP/QWP/1401/98)* and ethical principles stated of the *Declaration of Helsinki (Tokyo, 2004)*.

Results:

Table 1. Primary pharmaconiketic parameters of (R)-Lacosamide in study No. 16-003

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV %
$AUC_{(0\text{-}t)}$	98.18	95.32 - 101.11	5.68
C_{max}	103.19	95.19 - 111.85	15.60

The results indicated that the single dose of Test product is bioequivalent with single dose of Reference product in healthy male subjects under fasting condition.

Safety:

No death, serious or life-threatening adverse events (AEs) occurred during the study. No subject was withdrawn from the study for safety reason.

A total of three (3) AEs were observed in the study, involving two (2) subjects of 24 (safety set). In all cases the AEs were graded as 'mild' in intensity and considered 'unlikely' to be related to the study drug administered.

The Test- and Reference product were comparable in their safety and tolerability. Overall, the drugs investigated were well tolerated by subjects included in the study.

Conclusion on bioequivalence studies

Results derived from analysis of log-transformed primary efficacy parameters (C_{max}, $AUC_{0\text{-}t}$) for (R) - Lacosamide show that the Test/Reference ratios of LS (least-squares) mean values and their 90% confidence intervals also are entirely included within the acceptance range of 80.00% - 125.00%. Thus, results support the bioequivalence between the Test- and Reference treatments.

On the basis of results of bioequivalence study coded 16-003 the Lacosamide 200 mg film-coated tablets (manufactured by Genepharm S.A, Greece) (Test) and Vimpat® 200 mg film coated tablets (lacosamide) (manufactured by Aesica Pharmaceuticals GmbH, Germany, MAH: UCB Pharma S.A., Belgium (Reference) are bioequivalent in healthy adult subjects under fasting conditions.

Biowaiver:
The Applicant claimed for biowaiver for the dose strength of 50 mg, 100 mg and 150 mg on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).
Essential similarity was demonstrated by means of the pivotal bioequivalence study coded 16-003 between the Test- and Reference products. This study has demonstrated that a single dose of Applicant's Lacosamide 200 mg film-coated tablets (manufactured by Genepharm S.A., Greece) was bioequivalent to a single dose of Vimpat® 200 mg film coated tablets (lacosamide) (manufactured by Aesica Pharmaceuticals GmbH, Germany, MAH: UCB Pharma S.A., Belgium).
Qualitative compositions of the claimed strengths are same (50, 100, 150 and 200 mg), and quantitative compositions are proportionally similar.
Based on results of comparative dissolution test, similarity of dissolution profiles of the developed four dose-strength products (50 mg, 100 mg, 150 mg and 200 mg) was justified according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).
All general biowaiver criteria were fulfilled according to the recent bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).
Biowaiver claim for the 50 mg, 100 mg and 150 mg dose strengths was acceptable.

IV.3 Pharmacodynamics

There were no clinical pharmacology studies performed to evaluate the pharmacodynamics of Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets and none are required for applications of this type.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of lacosamide.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of lacosamide.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Risk Management Plan (version number: 0.4, Dated on: 14.12.2020)

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 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 pediatric population aged 4 to < 16 years

Pharmacovigilance Plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Losmorid 50, 100, 150 & 200 mg film-coated tablets.

As additional activity, the MAH encourages physician’s participation in the EURAP (International Registry of Antiepileptic Drugs and Pregnancy). The primary objective of the EURAP study is to collect data on lacosamide use in pregnancy or breastfeeding women.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Losmorid 50 mg, 100 mg, 150mg, 200 mg film-coated tablets.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.
Losmorid 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.

To support the application, the Applicant has adequately demonstrated bioequivalence between Losmorid 50 mg, 100 mg, 150mg, 200 mg film-coated tablets and VIMPAT 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets.

There were no objections against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets. The applicant and the future holder of authorisation is Alkaloid INT d.o.o.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator products were Vimpat 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets by UCB Pharma SA, authorised for marketing since 29 August 2008 in the European Union.

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

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Losmorid 50 mg, 100 mg, 150 mg, 200 mg film-coated tablets from Alkaloid INT d.o.o.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a bridging study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC.

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. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached