Public Assessment Report

Decentralised Procedure

Lacosamide Macleods 50 mg film-coated Tablets
Lacosamide Macleods 100 mg film-coated Tablets
Lacosamide Macleods 150 mg film-coated Tablets
Lacosamide Macleods 200 mg film-coated Tablets

(lacosamide)

UK/H/6861/001-004/DC

PL 34771/0246-0249

MACLEODS PHARMA UK LIMITED
LAY SUMMARY

Lacosamide/Macleods 50, 100, 150 and, 200 mg film-coated tablets (lacosamide)

This is a summary of the Public Assessment Report (PAR) for Lacosamide Macleods 50, 100, 150 and, 200 mg film-coated tablets. It explains how Lacosamide Macleods 50, 100, 150 and, 200 mg film-coated tablets were assessed, and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Lacosamide Macleods 50, 100, 150 and, 200 mg film-coated tablets.

These products will be referred to as Lacosamide film-coated tablets in this lay summary for ease of reading.

For practical information about using Lacosamide film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Lacosamide film-coated tablets and what are they used for?
These applications are for a generic medicines. This means that these medicines are the same as, and considered interchangeable with, the reference medicines already authorised in the European Union (EU) called Vimpat 50/100/150/200 mg film-coated tablets.

Lacosamide film-coated tablets are used in adults, adolescents and children aged 4 years and older 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 the brain. However, these may then spread to larger areas on both sides of the brain.

Lacosamide film-coated tablets may be used on its own or with other antiepileptic medicines.

How does Lacosamide film-coated tablets work?
Lacosamide film-coated tablets contains lacosamide which belongs to a group of medicines called “antiepileptic medicines”.

How is Lacosamide film-coated tablets used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is oral (by mouth).

Taking Lacosamide film-coated tablets:
- Lacosamide film-coated tablets should be taken twice a day – once in the morning and once in the evening.
- Patients should try to take it at about the same time each day.
- Lacosamide film-coated tablets tablet should be swallowed the with a glass of water.
- Lacosamide film-coated tablets can be taken with or without food.

The patient will usually start by taking a low dose each day and the doctor will slowly increase this over a number of weeks. When a dose is reached that works for the patient, this is called the “maintenance dose”, then the patient takes the same amount each day.

Lacosamide film-coated tablets is used as a long term treatment. The patient should continue to take Lacosamide film-coated tablets until their doctor tells them to stop.
For further information on how Lacosamide film-coated tablets is used, refer to the package leaflet and Summary of Products Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Lacosamide film-coated tablets have been shown in studies?
Lacosamide film-coated tablets are generic medicines that fulfil criteria meaning that no additional studies are required. Lacosamide film-coated tablets has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics. Further information is provided in the main body of the PAR.

What are the possible side effects of Lacosamide film-coated tablets?
Because Lacosamide film-coated tablets are generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary/Summaries of Products Characteristics (SmPC) available on the MHRA website.

Why was Lacosamide film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Lacosamide film-coated tablets has been shown to be comparable to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Lacosamide film-coated tablets?
A Risk Management Plan (RMP) has been developed to ensure that Lacosamide film-coated tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Lacosamide film-coated tablets
Marketing Authorisations for Lacosamide film-coated tablets were granted in the UK on 12 February 2019.

The full PAR for Lacosamide film-coated tablets follows this summary.

This summary was last updated in March 2019.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications Lacosamide Macleods 50, 100, 150 and, 200 mg film-coated tablets (PL 34771/0246-0249; UK/H/6861/001-004/DC) could be approved.

These products 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.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member States (CMSs) were Germany and Spain.

The active substance, lacosamide is a functionalised amino acid. The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilisation of hyperexcitable neuronal membranes.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines. The reference medicinal products are Vimpat 50/100/150/200 mg film-coated tablets, which were first granted in the EU to UCB Pharma SA, Belgium, registered in EU since August 2008 (EU/1/08/470/001-012 & 020-031).

No new non-clinical studies were conducted, which is acceptable given that the applications is/are based on being a generic medicinal products of a reference products that has/have been licensed for over 10 years.

A BCS class based biowaiver was sought for these applications, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this/these applications.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

The RMS and CMSs considered that the applications could be approved at the end of procedure (Day 210) on 15 January 2019. After a subsequent national phase, licences were granted in the UK on 12 February 2019.
II QUALITY ASPECTS

II.1 Introduction
These products consist of 50, 100, 150 or, 200 mg of the active substance lacosamide. In addition to lacosamide these products also contain the excipients:

Tablet core:
microcrystalline cellulose (101), microcrystalline cellulose (102), crospovidone type A, colloidal silicon dioxide, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate

Film-coat:
50 mg:
hypromellose 6mPas (E464), hypromellose 15mPas (E464), titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), polyethylene glycol 4000 (E1521), lecithin (E322), red iron oxide (E172), black iron oxide (E172), indigo carmine aluminium lake (E132).

100 mg:
hypromellose 6mPas (E464), hypromellose 15mPas (E464), titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), polyethylene glycol 3350 (E1521), lecithin (E322), yellow iron oxide (E172).

150 mg:
hypromellose 6mPas (E464), hypromellose 15mPas (E464), titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), polyethylene glycol 3350 (E1521), lecithin (E322), red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172).

200 mg:
hypromellose 6mPas (E464), hypromellose 15mPas (E464), titanium dioxide (E171), talc (E553b), polyvinyl alcohol (E1203), polyethylene glycol 3350 (E1521), lecithin (E322), indigo carmine aluminium lake (E132).

The finished products are packaged in clear PVC/PVdC- Aluminium blister pack in pack sizes of 14, 28, 56, 98 and 168 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
II.2 ACTIVE SUBSTANCE
rINN: Lacosamide
Chemical Name: 2R-2-(acetyl amino)-3-methoxy-N-(phenyl methyl) - propanamide.
Molecular Formula: C_{13}H_{18}N_{2}O_{3}
Chemical Structure:

\[\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Chemical structure of Lacosamide.}
\end{figure}}\]

Molecular Weight: 250.3
Appearance: A White to off white crystalline powder.
Solubility: Soluble in dichloromethane and methanol, sparingly soluble in water, sparingly soluble in ethanol at 25°C ±2°C.

Lacosamide is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.
No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

**Manufacture of the products**
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Products Specification(s)**
The finished products specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability**
Finished products stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage condition “Do not store above 30 °C” is acceptable.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
The grant of marketing authorisations is recommended.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of lacosamide are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

**III.2 Pharmacology**
No new pharmacology data were provided and none were required for these applications.

**III.3 Pharmacokinetics**
No new pharmacokinetic data were provided and none were required for these applications.

**III.4 Toxicology**
No new toxicology data were provided and none were required for these applications.

**III.5 Ecotoxicity/Environmental Risk Assessment**
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing authorisation for the proposed products.

**III.6 Discussion on the non-clinical aspects**
The grant of marketing authorisations is recommended.
IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of lacosamide is well known. According to the regulatory requirements, the applicant has provided an acceptable justification for BCS class based biowaiver and a bioequivalence study has not been required for these products. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics
No new pharmacokinetic data have been submitted for these applications and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Vimpat 50/100/150/200 mg film-coated tablets.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for these applications.

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 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

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with lacosamide is considered to have demonstrated the therapeutic value of the compound. These products are considered similar to the already authorised reference product and their benefit/risk is, therefore, considered to be positive.

The Summary of Products Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.
Lacosamide Macleods 150 mg film-coated tablets

MA Holder:
Macleods Pharma UK Limited
Wynyard Park House, Wynyard Avenue,
Wynyard, Billingham, TS22 5LB
United Kingdom
Code No.: HP115207
PL 34771/0046

1 film-coated tablet contains
150 mg lacosamide.

Oral use.
Read the package leaflet before use.

Place dispensary label here
TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the products licence are recorded in the current SmPC and/or PIL available on the MHRA website.

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<th>Products information affected</th>
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