Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

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

(lacosamide)

Product Licence Numbers: PL 16363/0570-0573

Milpharm Limited

LAY SUMMARY

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

(Lacosamide)

This is a summary of the Public Assessment Report (PAR) for Lacosamide Milpharm 50, 100, 150 and 200 mg film-coated tablets. It explains how Lacosamide Milpharm 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 Milpharm 50, 100, 150 and 200 mg film-coated tablets.

These products will be referred to as Lacosamide Tablets in this lay summary for ease of reading.

For practical information about using Lacosamide Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

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

Lacosamide tablets are used in adults, adolescents and children aged 4 years and Older in the treatment of epilepsy.

• 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 the brain. However, these may then spread to larger areas on both sides of the brain.

• Lacosamide Tablets may be used on its own or with other antiepileptic medicines.

How do Lacosamide Tablets work?
Lacosamide Tablets contain lacosamide. This belongs to a group of medicines called “antiepileptic medicines”.

How are Lacosamide Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

Lacosamide Tablets should be swallowed with a glass of water, with or without food.

This medicine must be taken twice each day, once in the morning and once in the evening, at about the same time each day.

Patients will usually start by taking a low dose each day and a 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. Lacosamide tablets are used as a long-term treatment. Patients should continue to take Lacosamide Tablets until a doctor

tells them to stop.

Adolescents and children weighing 50 kg or more and adults
The recommended starting dose of Lacosamide Tablets when it is taken on its own is 50 mg twice a day. A doctor may also prescribe a starting dose of 100 mg of Lacosamide Tablets twice a day.

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

The recommended starting dose of Lacosamide Tablets when taken with other antiepileptic medicines is 50 mg twice a day.

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

If patients weigh 50 kg or more, a doctor may decide to start Lacosamide Tablets treatment with a single "loading" dose of 200 mg. Patients would then start their ongoing maintenance dose 12 hours later.

Children and adolescent weighing less than 50 kg
The dose depends on the body weight. Patients 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.

A doctor may prescribe a different dose if patients have problems with their kidneys or with their liver.

For further information on how Lacosamide Tablets are used, refer to the package leaflet and Summaries of Product 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 Tablets have been shown in studies?
Because Lacosamide Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Lacosamide Tablets?
Because Lacosamide Tablets are generic medicines and are bioequivalent to the reference medicines, their 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 Summaries of Product Characteristics (SmPC) available on the MHRA website.

Why was Lacosamide Tablets approved?
It was concluded that, in accordance with EU requirements, Lacosamide Tablets have been shown to be comparable to and to be bioequivalent 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 Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Lacosamide Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs 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 Tablets
Marketing Authorisations for Lacosamide Tablets were granted in the UK on 07 May 2019.

The full Public Assessment Report (PAR) for Lacosamide Tablets follows this summary.

This summary was last updated in June 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 for Lacosamide Milpharm 50, 100, 150 and 200 mg film-coated tablets (PL 16363/0570-0573) could be approved.

The 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 active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide), 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 stabilization 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 and 200 mg film-coated tablets, which were first granted in the EU to UCB Pharma SA (EU/1/08/470/001-012 & 020-031) in August 2008.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being generic medicinal products of reference products that have been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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.

Marketing authorisations were granted for these products on 07 May 2019.

II QUALITY ASPECTS

II.1 Introduction

These products are of following description:

50 mg formulation
Light Pink to Pink coloured, oval shaped, film coated tablets debossed with “50” on one side and “LA” on the other side.

100 mg formulation
Light Yellow to Yellow coloured, oval shaped, film coated tablets debossed with “100” on one side and “L” and “A” on either sides of scoreline on the other side. The tablet can be divided into equal doses.

150 mg formulation
Light Orange to pinkish Orange coloured, oval shaped, film coated tablets debossed with”150” on one side and “L” and “A” on either sides of scoreline on the other side. The tablet can be divided into equal doses.

200 mg formulation
Light Blue to Blue coloured, oval shaped, film coated tablets debossed with “200” on one side and “L” and “A” on either sides of scoreline on the other side. The tablet can be divided into equal doses.

In addition to lacosamide, these products also contain the excipients cellulose, microcrystalline (Grade-101), low substituted hydroxy propyl cellulose, crospovidone (Type A), hydroxypropyl cellulose, cellulose, microcrystalline (Grade -102), silica, colloidal anhydrous and magnesium stearate making up the tablet core.

The tablet coating is composed of titanium dioxide (E 171), hypromellose (6 mPas) (E464), talc (E553b), poly vinyl alcohol (E1203), hypromellose (15mPas) (E464), macrogol 3350 (E1521), lecithin (Soya) (E322).

In addition, in their coating, the tablets of different strength contain the following.

- 50mg formulation: Iron Oxide Red (E172), Indigo Caramine AL [(3% - 5%) (E132)] and Black iron oxide (E172)
- 100mg formulation: Iron Oxide Yellow (E172)
- 150mg formulation: Iron Oxide Red (E172), Iron Oxide Yellow (E172) and Black iron oxide (E172)
- 200mg formulation: Indigo Caramine AL [(3% - 5%) (E132)] and Indigo Caramine Aluminium Lake [(11%- 14%) (E132)]

The finished products are packaged in clear polyvinylchloride (PVC), polyvinylidenechloride (PVdC) - aluminium foil blister packs. The pack sizes are 14 and 56 film-coated tablets.

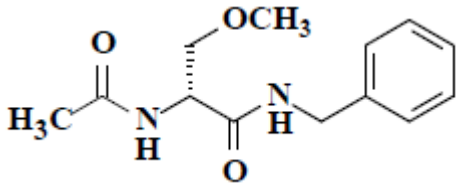
Not all pack sizes may be marketed.

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: (R)-2-Acetamido-N-benzyl-3-methoxypropionamide
(2R)-2-(Acetylamino)-3-methoxy-N-(phenylmethyl) propanamide
(R)-N-Benzyl-2-acetamido-3-methoxypropionamide
Molecular Formula: $C_{13}H_{18}N_2O_3$
Chemical Structure:



Molecular Weight: 250.29 g/mol
Appearance: A white or almost white or light yellow powder.
Solubility: Freely soluble in methanol, slightly soluble in acetonitrile and in ethanol and sparingly soluble in water.

Lacosamide is 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 has 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.

If appropriate: Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

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 Product Specifications
The finished product 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 product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions are acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

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
Either
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 Authorisations 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 are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

This study was an open label, balanced, randomised, two-treatment, two-sequence, two-period, crossover, single-dose oral bioequivalence study comparing the test product of Lacosamide 200 mg Tablets versus the reference products Vimpat 200 mg tablets (UCB Pharma SA, Belgium) in subjects under fasted conditions.

Subjects were administered a single dose of the test or reference product. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 8 days between the treatment periods. Sampling at 36.0, 48.0 and 72.0 hours were ambulatory collections.

A summary of the pharmacokinetic results are presented below:

Parameters	Ln-transformed Data		
	(A/B) % Ratio	90% Confidence Interval	Power (%)
C_{max}	97.19	90.69-104.16	100
AUC_{0-t}	98.24	95.16-101.42	100

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 200mg product strength can be extrapolated to the other strengths.

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

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

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 marketing authorisations is recommended for these applications.

V USER CONSULTATION

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Vimpat 50mg, 100mg 150mg and 200mg Film-coated Tablets (EMEA/H/C/000863; UCB Pharma SA) for the text and Metoprolol Aurobindo 50mg and 100mg Tablets (SE/H/1201/001-002/DC; Aurobindo Pharma Limited) for the design and layout. The bridging report submitted by the MAH is acceptable.

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. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

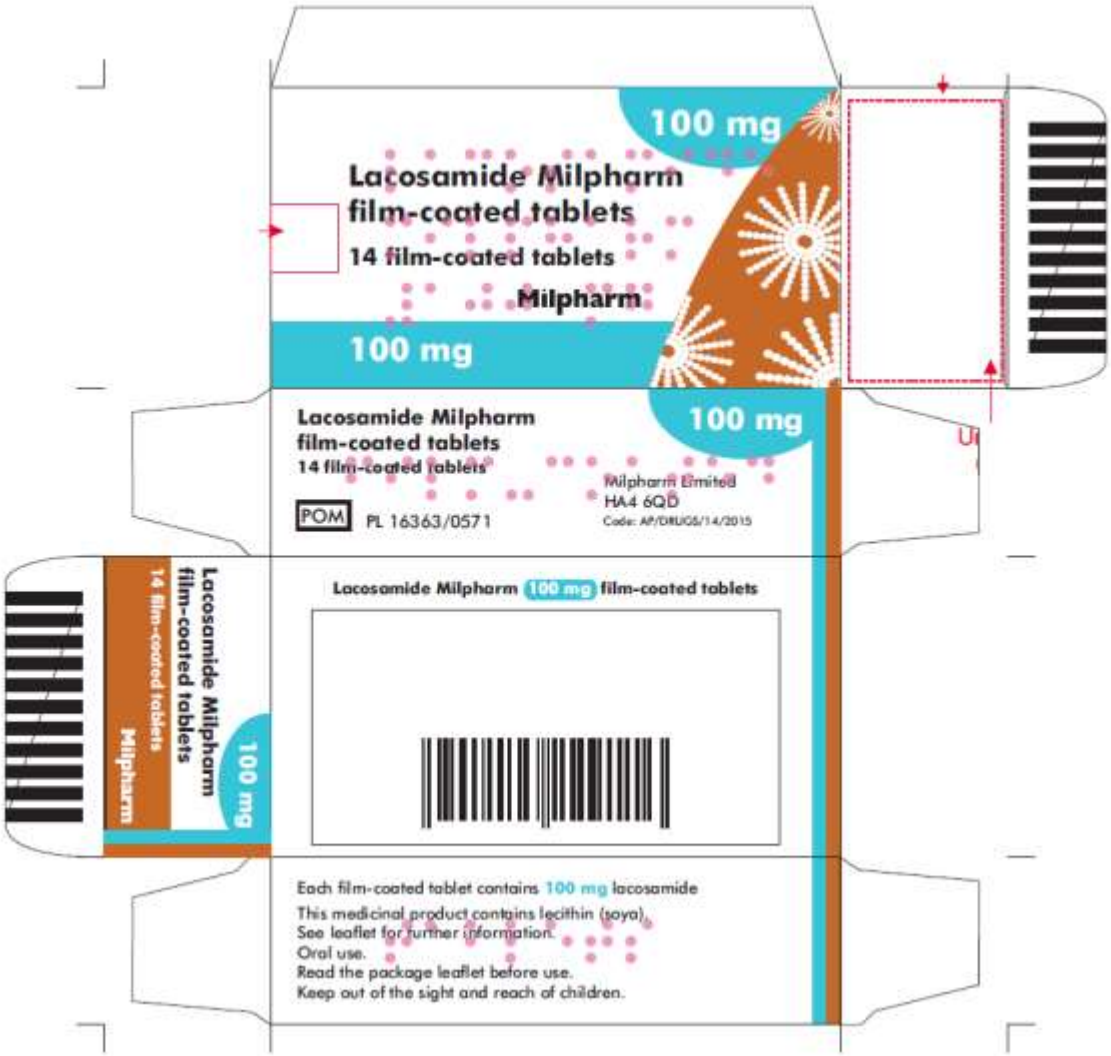
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

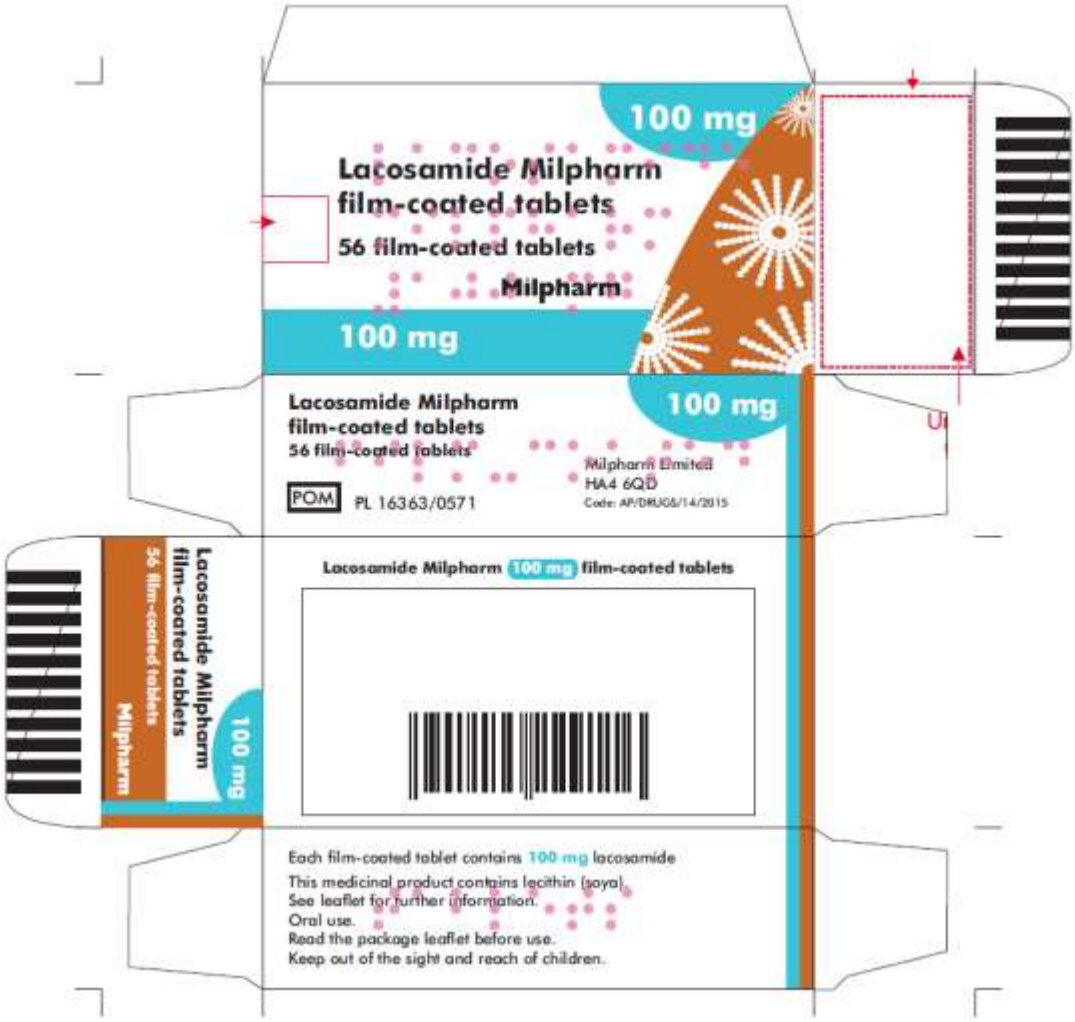
Representative copies of the labels at the time of UK licensing are provided below.


50 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
50 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
50 mg
Milpharm Limited
HA4 6QD
POM
PL 16363/0570
Lacosamide Milpharm 50 mg film-coated tablets
Each film-coated tablet contains 50 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.


50 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
50 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
50 mg
Milpharm Limited
HA4 6QD
Code: AP/DRUGS/14/2015
POM
PL 16363/0570
Lacosamide Milpharm 50 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
50 mg
Each film-coated tablet contains 50 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.


Lacosamide Milpharm 100 mg
film-coated tablets
Milpharm Limited
Lacosamide Milpharm 100 mg
film-coated tablets
Milpharm Limited
Lacosamide Milpharm 100 mg
film-coated tablets
Milpharm Limited
Code: AP/DRUGS/14/2015
Code: AP/DRUGS/14/2015
Lot: / EXP:
Lot: / EXP:
Lot: / EXP:
Lot: / EXP:


100 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
100 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
100 mg
POM
PL 16363/0571
Milpharm Limited
HA4 6QD
Code: AP/DRUGS/14/2015
Lacosamide Milpharm 100 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
100 mg
Each film-coated tablet contains 100 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.


100 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
100 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
100 mg
Milpharm Limited
HA4 6QD
Code: AP/DRUGS/14/2015
POM
PL 16363/0571
Lacosamide Milpharm 100 mg film-coated tablets
Each film-coated tablet contains 100 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.


Lot:
Lacosamide Milpharm 150 mg film-coated tablets
Milpharm Limited
EXP:
Code: AP/DRUGS/14/2015


150 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
150 mg
150 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
POM
PL 16363/0572
Milpharm Limited
HA4 6QD
Code: AP/DRUGS/14/2015
Lacosamide Milpharm 150 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
150 mg
Each film-coated tablet contains 150 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
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150 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
150 mg
150 mg
Lacosamide Milpharm
film-coated tablets
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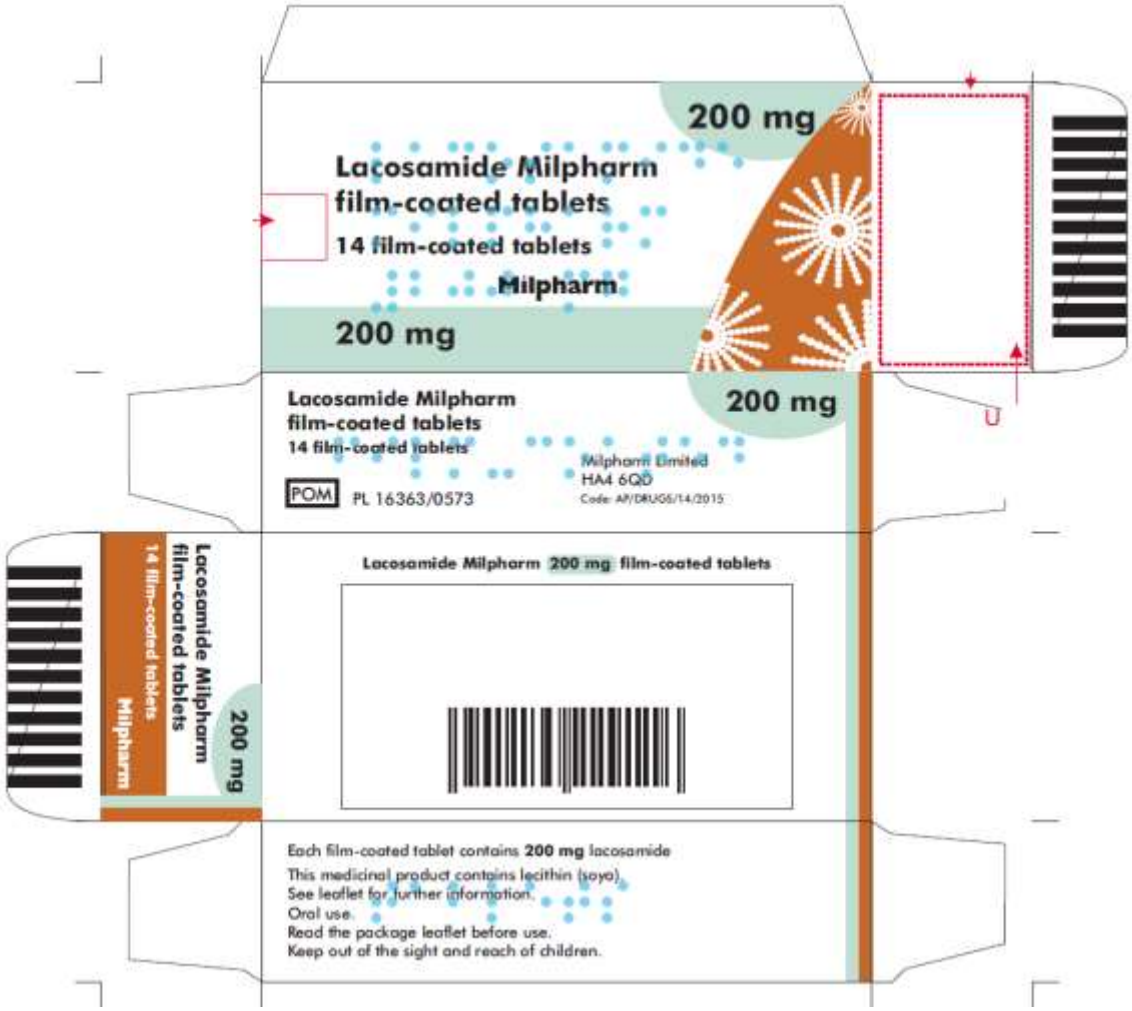
Milpharm Limited
HA4 6QD
POM
PL 16363/0572
Lacosamide Milpharm 150 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
150 mg
Each film-coated tablet contains 150 mg lacosamide
This medicinal product contains lecithin (soya).
See leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.


Lot:
Lacosamide Milpharm 200 mg film-coated tablets
Milpharm Limited
EXP:
Lot:
Lacosamide Milpharm 200 mg film-coated tablets
Milpharm Limited
EXP:
Lot:
Lacosamide Milpharm 200 mg film-coated tablets
Milpharm Limited
EXP:
Lot:
Lacosamide Milpharm 200 mg film-coated tablets
Milpharm Limited
EXP:
Lot:
Lacosamide Milpharm 200 mg film-coated tablets
Milpharm Limited
EXP:


200 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
200 mg
200 mg
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm Limited
HA4 6QD
Code: AP/DRUGS/14/2015
POM
PL 16363/0573
Lacosamide Milpharm 200 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
14 film-coated tablets
Milpharm
200 mg
Each film-coated tablet contains 200 mg lacosamide
This medicinal product contains lecithin (soya).
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200 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
200 mg
200 mg
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm Limited
HA4 6QD
POM
PL 16363/0573
Lacosamide Milpharm 200 mg film-coated tablets
Lacosamide Milpharm
film-coated tablets
56 film-coated tablets
Milpharm
200 mg
Each film-coated tablet contains 200 mg lacosamide
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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 product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of start of the procedure	Date of end of procedure	Outcome	Assessment report attached Y/N