20 July 2017
EMA/518597/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lacosamide Accord

International non-proprietary name: lacosamide

Procedure No. EMEA/H/C/004443/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human Use
CNS	Central Nervous System
ED_{50}	Median effective dose
LD_{50}	Median lethal dose
SmPC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 09 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Lacosamide Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Lacosamide Accord is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and literature from the reference medicinal product Vimpat instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Vimpat, 50mg, 100mg, 150mg, 200mg, film coated tablet
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 2 September 2008
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/08/470

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Vimpat, 50mg, 100mg, 150mg, 200mg, film coated tablet
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 2 September 2008
- Marketing authorisation granted by:

- Community
- Community Marketing authorisation number: EU/1/08/470

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

N/A

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 09 September 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 January 2017.
- During the meeting on 12 January 2017 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 May 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 June 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Scientific discussion

1.3. Introduction

This application concerns a generic medicinal product referring to the centrally authorised product Vimpat, which was first approved in the European Union on 29 August 2008.

The active substance is lacosamide, an amino acid derivate with anticonvulsive activity. Although its mechanism of action has not been fully elucidated, lacosamide has shown to selectively enhance slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyper-excitable neuronal membranes.

Vimpat was first approved as an adjunctive therapy for the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older. An extension of indication from add-on treatment to monotherapy was approved on 10 November 2016. At the time of this report, Vimpat was indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

Vimpat is available as tablets (50mg, 100mg, 150mg, and 200mg), solution for infusion (10mg/mL), and syrup (10mg/mL). Treatment is initiated at a starting dose of 50 mg twice a day which is titrated in weekly increments to a maximum maintenance dose of 200 mg twice a day for adjunctive treatment and 300 mg twice a day for monotherapy. In case of monotherapy, treatment can also be initiated at a starting dose of 100 mg twice a day. Vimpat may be taken with or without food.

The application for Lacosamide Accord concerns 50 mg, 100 mg, 150 mg and 200 mg film coated tablets, and approval is sought for the full range of indications for the reference product Vimpat at the time of this report. No clinical trials (bioequivalence studies) have been performed as a BCS (Biopharmaceutics Classification System) based biowaiver has been requested as per Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), which states that *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

1.4. Quality aspects

1.4.1. Introduction

The finished product is presented as film-coated tablets containing 50 mg, 100 mg, 150 mg and 200 mg of lacosamide as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, hydroxy propyl cellulose-L, hydroxy propyl cellulose (low substituted), colloidal anhydrous silica, crospovidone and magnesium stearate.

Tablet coat: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), lecithin (soya),

Strength 50 mg: iron oxide red (E172), iron oxide black (E172) and indigo carmine aluminum lake (E132).

Strength 100 mg: iron oxide yellow (E172).

Strength 150 mg: iron oxide red (E172), iron oxide black (E172) and iron oxide yellow (E172).

Strength 200 mg: indigo carmine aluminum lake (E132).

The product is available in PVC-PVDC/Aluminium blisters as described in section 6.5 of the SmPC.

1.4.2. Active substance

General information

The chemical name of lacosamide is (R)-2-acetamido-N-benzyl-3-methoxypropionamide corresponding to the molecular formula $C_{13}H_{18}N_2O_3$ and has a relative molecular mass 250.30 g/mol and has the following structure:

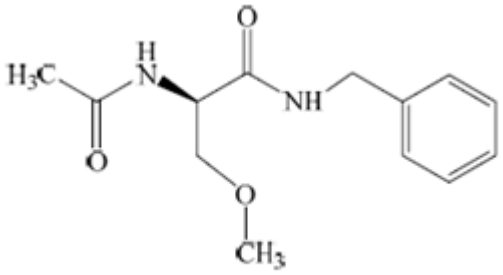

Figure 1 – Structure of lacosamide

The confirmation of the chemical structure has been conducted based on IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectroscopy

The active substance is a white to light yellow powder, non-hygroscopic, and soluble in methanol, sparingly soluble in water and slightly soluble in acetonitrile and ethanol**.**

Lacosamide exhibits stereoisomerism due to the presence of one chiral centre. Therefore, two isomers are possible, i.e. R-isomer and S-isomer. The desired isomer is R-isomer and the undesired S-isomer is controlled in the active substance specification by HPLC with a limit of not more than 0.15 % in line with the ICH Q3A Guideline.

Since, according to literature, lacosamide exhibits polymorphism (four crystalline forms are possible), XRD and DSC studies were done to confirm the polymorphic form of lacosamide manufactured by the ASMFH. Results of XRD data and DSC data of three commercial scale batches showed that polymorphic Form-I is consistently produced.

Manufacture

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Lacosamide is manufactured by non-sterile and non-aseptic process in an active substance manufacturing facility.

Lacosamide is synthesized in 5 main stages following by purification of the active substance using commercially available well defined starting materials with acceptable specification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The audit of the active substance manufacturer/s and intermediate manufacturer/s have been carried out by the ASMF holder or active substance manufacturer itself and thus the CHMP was of the opinion that they cannot be listed as a contract acceptor in the QP declaration due to possible conflict of interest. Therefore, the CHMP recommended the 3 QP declarations should thus be revised accordingly and to provide adequate justification from all 3 QPs involved that they are satisfied with audit results in spite of potential conflict of interest and respective authorities to look into the issue at the next re-inspection of these sites in question. This should be provided before the marketing of the product.

The active substance is packaged in transparent polyethylene bag and tied with strip seal, which is placed in another transparent polyethylene bag and tied with strip seal. Finally packed material placed in HDPE drum, the lid of the drum is closed by a clamp. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), solubility (Ph. Eur.), identification (IR, HPLC, XRD), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), specific optical rotation (Ph. Eur.), chiral related substances (HPLC), enantiomeric purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), appearance of solution (Ph. Eur.), dimethyl sulfate content (HPLC), acetic acid content (GC), particle size (Malvern Analyzer), and microbial examination (Ph. Eur.).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (6 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 5 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 48 months under long term conditions at 25 ºC / 60% RH and for up

to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, water content, chiral related substances, enantiomeric purity, related substances, assay, and appearance of solution.

All principal physical and chemical parameters were well within the proposed limits during the accelerated and long term storage conditions without showing any sign of degradation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when preserve in tight containers and store at 25°C, with excursions permitted to 15°C – 30°C in the proposed container.

1.4.3. Finished medicinal product

Description of the product and Pharmaceutical development

Lacosamide tablets are presented in four strengths; 50 mg, 100 mg, 150 mg and 200 mg. The finished product is presented as follows:

Lacosamide 50 mg film-coated tablets: pink, oval, coated tablets, debossed “L” on one side and “50” on other side.

Lacosamide 100 mg film-coated tablets: dark yellow, oval, coated tablets, debossed “L” on one side and “100” on other side.

Lacosamide 150 mg film-coated tablets: salmon, oval, coated tablets, debossed “L” on one side and “150” on other side.

Lacosamide 200 mg film-coated tablets: blue, oval, coated tablets, debossed “L” on one side and “200” on other side.

The aim of the development was to formulate a robust, physicochemically similar, stable, dose weight similar and bio-waiver compliant (based on BCS class I) generic formulation of Lacosamide 50/100/150/200 mg film-coated tablets, compared to the reference product Vimpat. This was achieved by developing a stable formulation and carrying out dissolution profile matching of the generic and reference medicinal products.

Various physical and chemical properties of the active substance are affected by their particle size, distribution and shape. The effect is not only on the physical properties of the solid but also their biopharmaceutical behaviour, content uniformity, solubility and stability. As shown in literature information, the active is classified as highly soluble (BCS class I) and particle size does not have any impact on dissolution. The particle size is not expected to impact the quality of product. The solubility of lacosamide at different pH range of the gastrointestinal tract was determined to aid in selecting suitable dissolution media for development purpose and to ensure that ‘sink conditions’ are maintained therein. Minimum solubility to claim the sink condition for lacosamide is 0.667 mg/ml. The pH solubility profile indicates that the lacosamide is highly soluble and sink conditions are possible throughout the gastro-intestinal pH range.

A compatibility study of lacosamide with different excipients (including those used in the reference product) was carried out by accelerated thermal stress study. Compatibility studies were carried out using different active substance and excipients ratio. No significant changes were observed. Hence, based on the active substance - excipients compatibility study results, it can be concluded that lacosamide is compatible with the studied excipients.

Excipients considered for the generic medicinal product were selected based on reference medicinal product and active substance-excipient compatibility study. All the excipients are tested and found to comply with current individual Ph. Eur. monograph / EU directive and film-coating materials are tested and found to comply with in-house specification. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product development trials were initiated considering the below requirements:

1) Bio-waiver strategy (as it is a BCS class I active substance, lacosamide has been proven to exhibit high solubility and complete absorption).

2) Similarity in dissolution profile at pH 1.2 (0.1N HCl), Acetate buffer pH 4.5 and Phosphate buffer pH 6.8 when compared to the reference medicinal product, Vimpat.

Lacosamide exhibits poor flow properties. As this may impact the quality parameters of the product direct compression approach was not considered suitable for manufacture of lacosamide tablets. Hence, it was decided to use wet granulation approach for the manufacturing of the finished product.

The formulation was optimised for the functional excipients by varying its concentration of finalised limits as established in developmental trials. The formulation optimisation trials have been conducted on the higher strength, i.e. 200 mg. The trials were carried out to optimise the concentration of functional excipients used in the formulation.

No clinical trials (i.e. bioequivalence studies) have been carried on the product as a *BCS based biowaiver* is requested for lacosamide film-coated tablets as per Appendix III of guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

As per the guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Applying for a BCS based bio-waiver is restricted to highly soluble active substances with known human absorption, which are considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

It has been demonstrated in this case that the BCS based bio-waiver is applicable because the active substance (lacosamide) has been proven to exhibit high solubility and complete absorption (BCS class I) and not have a narrow therapeutic index, very rapid (more than 85 % within 15 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated across the required pH range and excipients that might affect bioavailability are qualitatively the same in both test and reference product. Moreover, the impurity profile of the generic finished product was compared with the impurity profile of reference product. The impurity profile was found to be similar to that of the reference product. As no additional impurities observed in test product, it can be considered to be essentially similar to the reference product.

As demonstrated by the pH solubility profile study, lacosamide is BCS class I molecule have high solubility and sink condition is possible across the pH range of 1.2 to 7.5. After considering solubility and pharmacokinetic behaviour, 0.1N HCl medium was selected for routing testing of lacosamide tablets.

The multimedia dissolution profile comparison was performed on following dissolution media: 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer

The discriminatory nature of the selected dissolution method was demonstrated.

To optimize the manufacturing process parameters, the trials were carried out for manufacturing of the finished product.

The primary packaging is PVC-PVDC/Aluminum blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps: granulation, drying, sizing, blending (lubrication), compression and film-coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), average weight of tablet, identification (HPLC, IR, Chiral method), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution, related substances (HPLC), assay (HPLC), and microbial examination (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 production scale batches for each strength of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same specifications as release. The analytical procedures used are stability indicating.

The tests performed during long term and accelerate stability studies complied with the specifications and well within the acceptance criteria.

Stability data of 2 production scale batches for each strength of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in polypropylene copolymer (PPCP) container which is the transportation/bulk storage pack. The tests performed during long term and accelerated stability studies complied with the specifications and results were well within the acceptance criteria. Based on satisfactory stability data on PPCP container, 12 month storage period is assigned for PPCP container.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed, therefore, it was concluded that the film-coated tablets are photo-stable.

Forced degradation study was carried out to identify the likely degradation products and to validate the stability indicating power of the analytical procedures by using forced degradation samples. The degradation study was carried out on 50 mg strength and is considered applicable for other strengths. The degradation conditions used were: acid degradation (1M HCl at 60°C for 24 hours), base degradation (1M NaOH at room temperature for 18 hour), oxidation degradation (30% H_2O_2 at 60°C for 24 hours), thermal degradation (105°C for 72 hours), UV degradation and water hydrolysis (water at 60°C for 72 hours).

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

1.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

1.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

1.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The audit of the active substance manufacturer/s and intermediate manufacturer/s have been carried out by the ASMF holder or active substance manufacturer itself and due to possible conflict of interest they cannot be listed as a contract acceptor in the QP declaration. Therefore, the 3 QP declarations should thus be revised accordingly and to provide adequate justification from all 3 QPs involved that they are satisfied with audit results in spite of potential conflict of interest and respective authorities to look into the issue at the next re-inspection of these sites in question. This should be provided before the marketing of the product.

1.5. Non-clinical aspects

1.5.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

1.5.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Lacosamide Accord is considered unlikely to result in any significant increase in the combined sales volumes for all lacosamide containing products and the exposure of the environment to the active substance. Thus, the Environmental Risk Assessment is expected to be similar and not increased.

1.5.3. Discussion and conclusion on non-clinical aspects

The non-clinical overview adequately discusses pharmacological and toxicological literature. No issues were raised with respect to the excipients or impurities. All non-clinical information has been adequately reflected in the SmPC in line with the reference product.

Therefore, the CHMP agrees that Lacosamide Accord is approvable from a non-clinical point of view.

1.6. Clinical aspects

1.6.1. Introduction

This is an application for a generic product consisting of film-coated tablets containing 50 mg, 100 mg,

150 mg and 200 mg of lacosamide. No bioequivalence studies have been carried as a BCS-based biowaiver has been requested.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of lacosamide based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

In line with Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. BCS based biowaivers are restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

The applicant has submitted a BCS Class I based biowaiver request for which the following requirements must be met:

- The drug substance has been proven to exhibit high solubility and complete absorption (BCS class I), and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product have been demonstrated, and
- excipients that might affect bioavailability are qualitatively and quantitatively the same.

The applicant's justification for the applicability of the bio-waiver to lacosamide film-coated tablets is summarised below:

1. Drug substance

Lacosamide is not considered a narrow therapeutic index drug based on the following evidences:

- Treatment emergent adverse events reported during long-term open-label trials did not differ from those reported in shorter-term randomized trials, suggesting that long-term lacosamide therapy is not associated with emergence of unexpected adverse events, and that the incidence of overall adverse events does not increase with continuing exposure to lacosamide.
- The median effective dose (ED_{50}) value in rats against tonic-extension seizures induced by the maximal electroshock seizure is 3.9 mg/kg, p.o. (Beyreuther BK et al. 2007). The estimated median lethal dose (LD_{50}) value in rats is 253 mg/kg, p.o. respectively (Product monograph Vimpat®). The difference between the LD_{50} and ED_{50} is large.

Lacosamide has been shown to exhibit high solubility and complete absorption in line with BCS class I. Solubility has been tested in different media with different pH. These data show that a single dose of 200 mg in an immediate release formulation is completely dissolved in 250 ml of buffers within the pH range of 1 – 7.5 at 37±1°C. Furthermore, lacosamide is rapidly and completely absorbed after oral administration of the tablets with a bioavailability of approximately 100%. Hence, lacosamide shows high permeability.

2. Drug product

The applicant has provided *in vitro* dissolution data investigating the similarity of dissolution profiles between test product (lacosamide film-coated tablets 50/100/150/200mg; manufactured by Intas Pharmaceutical Ltd, India) and reference product (Vimpat® 50/100/150/200mg film-coated tablets marketed by UCB Pharma SA, Belgium) in different dissolution media. Different batches of the test and reference product for all 4 strengths were used.

The dissolution conditions and method used were in line with Appendix III of the Guideline on Bioequivalence and are presented below:

Apparatus:	Paddle
Volume of dissolution medium:	900 ml
Temperature of dissolution medium:	37±0.5 °C
Agitation speed:	50 rpm
Sampling schedule:	10, 15, 20, 30 and 45 min
Buffer:	(a) 0.1 N HCl
	(b) pH 4.5 acetate buffer
	(c) pH 6.8 phosphate buffer

From the comparative dissolution study, lacosamide film-coated tablets showed very rapid (more than 85% within 15 min) *in vitro* dissolution characteristics for both the rest and reference product for all three buffers/pH. The results were consistent across all batches analysed.

3. Excipients

The excipients used in the test product (lacosamide film-coated tablets 50/100/150/200 mg; manufactured by Intas Pharmaceutical Ltd, India) and the reference product (Vimpat® 50/100/150/200mg film-coated tablets marketed by UCB Pharma SA, Belgium) are qualitatively the same, except for Lecithin (soya), which is only present in the film-coating of Lacosamide Accord tablets. The quantitative differences of the excipients were considered unlikely to affect the bioavailability of lacosamide. All of the excipients are well established and are used at concentrations commonly used in the preparation of immediate release tablets. At these concentrations none of the excipients is expected to affect the oral bioavailability of lacosamide. Furthermore, there is no safety or clinical concern regarding the presence of any of these excipients in this formulation. This was agreed by the CHMP, who also agreed that the change in the coating components compared to the reference product would not affect the bioavailability of lacosamide.

1.6.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

1.6.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

1.6.4. Discussion on clinical aspects

This marketing authorisation application for Lacosamide Accord is a generic application referring to the centrally authorised product Vimpat. As such, no new efficacy or safety studies have been conducted and are not required. Furthermore, no bioequivalence study was performed on the product due to a BCS-based biowaiver as per Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The applicant demonstrated that lacosamide is highly soluble and the oral bioavailability is approximately 100%. Furthermore, lacosamide is considered a broad therapeutic index drug and *in vitro* dissolution data showed very rapid dissolution characteristics for both Lacosamide Accord and Vimpat® film-coated tablets (more than 85% within 15 min). Finally, the excipients in the generic medicinal product at the concentrations used were considered unlikely to affect the oral bioavailability of lacosamide.

1.6.5. Conclusions on clinical aspects

Based on the available data, the CHMP considered that all criteria for a BCS-based biowaiver were met. Therefore the absence of a bioequivalence study was considered justified and the CHMP concluded that no clinical data were needed to support the application for Lacosamide Accord 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets as a generic medicinal product to Vimpat.

1.7. Risk management plan

Safety concerns

Table 7 – Summary of the 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	• Hepatotoxicity • Worsening of seizures • 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

	• Pediatric patients aged below 16 years

Pharmacovigilance plan

Table 8 – On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study conducted by EURAP - An International Registry of Antiepileptic Drugs and Pregnancy (Category 3)	The primary objective of the study is to collect data on lacosamide use in pregnancy or breastfeeding women and to address missing information on the use of lacosamide in pregnant or breastfeeding women	Pregnant or lactating women	Planned; Tentatively by Q4-2017	The requirements for submission of periodic safety update reports for this medicinal product will be followed as 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.

Risk minimisation measures

Table 9 - Summary table of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Cardiac AEs that may be potentially associated with PR interval prolongation and sodium channel modulation	Wording in SmPC sections 4.3, 4.4, 4.5, 4.8, 4.9 and 5.3 and corresponding section of PIL. "Prescription only" product	None
Suicidality	Wording in SmPC sections 4.4 and 4.8 "Prescription only" product	None
Dizziness	Wording in SmPC sections 4.4, 4.7, 4.8 and 4.9 "Prescription only" product	None
Important potential risks		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	Wording in SmPC sections 4.8 and 5.3 “Prescription only” product	None
Worsening of seizures	Wording in SmPC sections 4.9. “Prescription only” product	None
Abuse as a CNS-active product	Wording in SmPC section 4.8 of lacosamide SmPC and corresponding section of PIL Package Size: Lacosamide Accord film coated tablets is available in packs of 14, 56, 60 or 168 tablets. Packs of 14 x 1 or 56 x 1 tablet is available in perforated unit dose blisters. “Prescription only” product	None
Potential for off-label use of a loading dose in acute conditions such as status epilepticus	Wording in SmPC section 4.2 of and corresponding section of PIL “Prescription only” product	None
Missing Information		
Pregnant or lactating women	Wording in SmPC section 4.6 and 5.3 “Prescription only” product	None
Pediatric patients aged below 16 years	Wording in SmPC section 4.2 and 4.8 of lacosamide SmPC and corresponding section of PIL “Prescription only” product	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4.0 (dated 21 June 2017) is acceptable.

1.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product 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.

1.9. Product information

1.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vimpat. The bridging report submitted by the applicant has been found acceptable.

2. Benefit-risk balance

This application concerns a generic version of lacosamide film-coated tablets (50 mg, 100 mg, 150 mg, 200 mg). The reference product Vimpat is indicated as monotherapy or adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adult and adolescent (16-18 years) patients with epilepsy.

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics nor the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Furthermore, no bioequivalence study was conducted since the product met the criteria for a BCS-based biowaiver in accordance with Appendix III of the Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

A benefit/risk balance comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

3. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the benefit-risk balance of Lacosamide Accord is favourable in the following indication:

“Lacosamide Accord is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.”

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product 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. In this case, no PSUR submissions are requested.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.