EMA/305791/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimpat

lacosamide

Procedure No.: EMEA/H/C/000863/X/0027

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma SA submitted on 5 August 2011 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Vimpat 10 mg/ml Syrup in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older through the centralised procedure falling within the Article 19 (1) and Annex I point 2 indent c) of Commission Regulation (EC) No 1234/2008.

UCB Pharma SA is already the Marketing Authorisation Holder for Vimpat 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets and 10 mg/ml solution for injection EU/1/08/470/001 – 013, and -016-017.

The applicant applied for the following indication: Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

The legal basis for this application refers to:

Article 19 (1) and Annex I (point 2 intend c) of the Commission Regulation (EC) No 1234/2008.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

At time of the initial submission of this extension application Art. 8 of Regulation (EC) No 1901/2006 did not apply (no new indication, no new route of administration, and no new pharmaceutical form).

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.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Vimpat has been given a Marketing Authorisation in the USA on 20 April 2010.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: **Tomas Salmonson**

- The application was received by the EMA on 5 August 2011.
- The procedure started on 21 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2011. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur declared that he had completed the assessment report in less than 80 days.
- During the meeting on 17-20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 November 2011.
- During the meeting on 12-15 December 2011, 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 Authorisation to Vimpat 10 mg/ml Syrup on 15 December 2011.

2. Scientific discussion

2.1. Introduction

Vimpat was initially approved on 29 August 2008 as 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets, 15 mg/ml syrup and 10 mg/ml solution for injection. It is indicated for use as adjunctive treatment in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsant drug candidates. Lacosamide has demonstrated antiepileptic activity in different rodent seizure models for generalized and complex partial-onset seizures and status epilepticus, i.e. maximal electroshock seizures (MES), hippocampal kindling, audiogenic seizures (AGS), self sustaining status epilepticus (SSSE), and in 1 chemoconvulsant-induced seizure model. It is also effective in animal models of neuropathic pain. Electrophysiological studies have shown that lacosamide enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces hyperexcitability of neurons characteristic for both epilepsy and neuropathic pain.

The MAH applied for an extension to the marketing authorization in order to introduce the 10 mg/ml lacosamide syrup. The application for MA of the 10 mg/ml syrup has been triggered by the fact that the former 15 mg/ml syrup had shown to be prone to precipitation of the active substance upon storage. The reason for this is that the 15 mg/ml syrup was supersaturated with respect to lacosamide. The 15 mg/ml syrup batches were withdrawn from the market and an Article 20 referral was initiated to review the risk-benefit of the product. The 15 mg/ml syrup was deleted from the Marketing Authorisation on 24 November 2011. The 10 mg/ml syrup is intended to provide a liquid oral formulation to patients who have difficulties in swallowing and to replace the 15 mg/ml syrup.

2.2. Quality aspects

2.2.1. Introduction

The approved commercial dosage forms for Vimpat are 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets, and 10 mg/ml solution for injection. The subject of this line extension is the additional 10mg/ml strength syrup. The formulation is qualitatively identical to the former 15 mg/ml syrup but quantitatively different.

Vimpat 10 mg/ml syrup is a slightly viscous, clear, colourless to yellowish or yellowish-brown liquid packed in amber glass bottles with white polypropylene screw caps of 200 ml and 500 ml, filled with 200 ml and 465 ml of product, respectively.

2.2.2. Active Substance

The active substance used in the new strength is the same as that used in the manufacture of the already approved formulations of Vimpat. There were no changes made to active substance and therefore no additional data was submitted. The CHMP endorsed this approach.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Lacosamide is a white to light yellow non-hygroscopic powder with a melting range of 140-146°C. It can be considered a stable substance and the approved re-test period is 4 years.

Log P (octanol/water) for lacosamide is estimated at 0.25. No pKa-value has been found in the pH range 1.5-12.3. The permeability of lacosamide has been investigated in absolute bioavailability studies and by in vitro experiments with propranolol as highly permeable reference standard across a monolayer of epithelial cells (Caco-2 monolayer). The results show that lacosamide can be considered a highly permeable substance with significantly higher permeability than the propranolol reference.

Four crystalline forms and one amorphous form of lacosamide have been identified and characterised. The synthesis process provides a mixture of the crystalline Form 1 and Form 2 which have similar properties (e.g. regards solubility). The solubility of Form 1 and Form 2 have been investigated in aqueous media in the pH range 1-7.5 where lacosamide is sparingly soluble. The lowest solubility determined at 25°C in these experiments was 20 mg/ml (Form 1:20.1 mg/ml and Form 2:20.8 mg/ml. The Applicant therefore regards the presence of either polymorph in the product at a concentration of 10 mg/ml as non critical. Solubility testing at room temperature by supersaturation of the formulation confirmed that 17.1 mg of lacosamide can be dissolved in 1 ml of the matrix vehicle.

Based on the high permeability and found sufficiently high solubility, the Applicant considers lacosamide as a BCS Class 1 substance.

The particle size of lacosamide is not considered a critical parameter since the substance is completely dissolved in the formulation.

The excipients of the product have been chosen with the aim to provide an acceptably tasting and stable product. The product contains a number of taste modifying agents, solubiliser/thickener, antimicrobial preservative and purified water. The excipients are qualitatively identical to those of the current 15 mg/ml syrup.

The aim of the pharmaceutical development was to overcome the strong bitter taste of the drug substance. The sweeteners sorbitol and acesulfame potassium were included in the formulation since bitterness and sweetness will mutually suppress each other. Sodium chloride is added to further suppress bitterness but without impacting sweetness. In addition, two flavouring agents, strawberry flavour 501440 T and the bitter masking flavour 501521 T were included in the formulation. The combination of these two flavouring agents was found to be superior to other combinations of masking agents. The ingredients of the flavours comply with Directive 88/388 and are listed in the European Register of flavouring substances used in or on foodstuffs.

An increase in viscosity, as accomplished by glycerol, carboxymethylcellulose and macrogol 4000, further reduces bitterness as a result of lower diffusion rate of lacosamide to the taste buds.

It was found that the addition of preservative was needed to ensure the microbiological quality of the drug product. Thus, the antimicrobial preservative sodium methyl parahydroxybenzoate (2.60 mg/ml) is added to the formulation to inhibit microbiological growth. Purified water is used as solvent and citric acid is included to adjust the pH of the formulation to a physiologically well-tolerated range, 3.8-5.0.

All excipients, except for the flavouring agents, are described in the Ph Eur and they comply with their respective monographs therein.

The syrup formulation was developed to provide a dosage form for patients with difficulties in swallowing tablets. Initially the 10 mg/ml strength of lacosamide was intended but in order to reduce the necessary volume to be taken by the patient, the 15 mg/ml strength was developed and subsequently approved.

In Q3 2010 a quality defect in the 15 mg/ml lacosamide syrup was reported. A flake-like precipitate was observed in the product which was identified as the active substance lacosamide. New solubility investigations revealed that the 15 mg/ml syrup is actually supersaturated with respect to lacosamide in the vehicle and that precipitation may occur in an unpredictable way during storage in any batch. Furthermore, homogeneity of the liquid phase in the bottles could not be demonstrated and the risk of incorrect dosing was acknowledged. This quality defect of the 15 mg/ml syrup triggered the current Marketing Authorisation Application for the lower strength, 10 mg/ml.

Further solubility studies were performed and the thermodynamic activity of lacosamide in placebo matrixes of syrup was investigated. The results showed that the saturated solidity of lacosamide in the syrup matrix is above 10 mg/ml and therefore the risk fro precipitation is no longer present. However, since the saturated solubility at 5^{o}C is close to the proposed syrup concentration of 10 mg/ml, the MAH will perform stability studies on the proposed formulation at refrigerated conditions to evaluate if a temperature storage precaution is necessary and as a precautionary measure, a warning has been added to the PI ("Do not refrigerate").

Biowaiver

In the original application for the 15 mg/ml syrup, a bioequivalence study was submitted which demonstrated bioequivalence between film-coated tablets (used in clinical studies) and a 10 mg/ml syrup formulation. A biowaiver for the 15 mg/ml syrup was requested and granted on the basis that the lacosamide is in solution in the syrup and the composition with respect to excipients was regarded as similar in the two strengths. For the 10 mg/ml strength of the current application, a biowaiver was also requested based on the same bioequivalence study. To support the request for the biowaiver the following justifications have been provided:

- the active substance is completely in solution in the product,
- the highest strength is soluble in ≤250 ml of aqueous media in the pH range 1 to 7.5,

- the active substance is considered highly permeable having linear and complete absorption, about 95% after oral administration.
- the qualitative composition of the 10 mg/ml syrup used in the bioequivalence study and the 10 mg/ml formulation currently proposed for marketing are considered similar and the minor differences are not expected to have any influence on the bioavailability.

The request for a biowaiver for the 10 mg/ml lacosamide formulation with the proposed composition can therefore be granted.

Adventitious agents

The drug substance and all excipients are free of materials of human or animal origin.

Manufacture of the product

Vimpat syrup 10mg/ml is manufactured by two different manufacturers. There are some minor differences in the manufacturing process at the two proposed manufacturing sites.

The manufacturing process is considered standard for this pharmaceutical form. The manufacturing process comprises the following major steps: (1) Dispersion of carboxymethylcellulose sodium in glycerol and part of the water, (2) Addition of sorbitol and macrogol 4000 (3) Addition and dissolution of lacosamide at 40-60°C (4) Addition of sodium chloride, citric acid and acesulfame potassium (5) Cooling the solution (6) Addition of antimicrobial preservative, flavours and the remaining quantity of purified water (7) Filtration and transfer into suitable polyethylene-coated fiberboard drums to the filling line (8) Filling.

No critical steps have been identified but a number of stages are monitored by process controls to ensure process integrity. These include dispersion of carboxymethylcellulose sodium in glycerol, addition of lacosamide under heating, cooling the solution after dissolution of lacosamide, final volume adjustment, filtration of the solution, content and homogeneity of lacosamide in the syrup after filtration, checking the fill volume and cap torque check.

Process validation has been conducted for the compounding step and the packaging steps will be validated post-approval.

Product specification

Adequate release and shelf-life specifications were validated for the drug product and include tests for: appearance (primary packaging material and contents of bottle), odour, colour, clarity, identity of lacosamide (HPLC and UV), identity of preservatives (HPLC), identity of flavouring agents and masking flavour (HPLC), purity (HPLC), pH, assay of lacosamide (HPLC),assay of the preservative (HPLC), microbiological purity (PhEur). Impurity limits in the specification are justified by toxicology studies. The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analyses data has been provided for three production scale batches form each of the manufacturers of the finished product. All batches complied with the set acceptance criteria.

The proposed specifications are considered justified. The analytical methods have been validated according to ICH guidelines, where necessary. Batch analysis data for the finished product have been provided from both manufacturing sites. The batches have been tested by the release testing site approved for testing the product in the US, but the results are reported against the proposed specifications of the current application.

Stability of the product

Stability studies according to ICH guidelines have been initiated on three batches of the finished product (two of the batches are production scale and one batch is pilot scale). The finished product is packaged in 200 ml and 500 ml amber glass bottles which are stored both upright and horizontally. The storage conditions are long term 25°C/60% RH and accelerated 40°C/75% RH. The accelerated studies have been completed and 24 months of long term data are currently available. No significant changes have been observed with respect to any of the parameters studied and all results are within proposed specifications. The product batches complied with Ph Eur 5.1.3 requirements for preservative effectiveness. The microbial purity was also within specifications at all instances.

A freeze-thawing study of product samples showed that upon thawing, there was some segregation of lacosamide substance in the bottles (more lacosamide in the bottom of the bottle and less at the top). If the bottles were shaken after thawing, the segregation of lacosamide disappeared. The results of the freeze-thawing study, and the previous experience with precipitation in the 15 mg/ml syrup, suggests that a formal primary stability study at the refrigerated condition should be conducted in order to elucidate if there is a need for a storage precaution against lower temperatures. Nonetheless, as a precautionary measure, a warning has been added to the product information ("Do not refrigerate").

An in-use stability study has also been conducted. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are accepted.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The finished product is an oral solution. The critical feature of the drug product is the limited solubility of lacosamide. It has been shown that the product is stable at long term and accelerated ICH conditions. The concentration of the preservative has been justified.

The request for a biowaiver for the 10 mg/ml lacosamide formulation with the proposed composition can be accepted from a pharmaceutical point of view. The 10 mg/ml lacosamide oral liquid formulation used in the bioequivalence study against the film-coated tablets has a composition which is sufficiently similar to the current 10 mg/ml product and a biowaiver can therefore be granted.

2.2.5. 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.

2.3. Non-clinical aspects

No new non-clinical data were provided for this application. The CHMP considered that no additional non-clinical information was required in order to support benefit/risk evaluation of the 10 mg/ml syrup.

2.4. Clinical aspects

2.4.1. Introduction

No new clinical data were provided for this application. The CHMP considered that no additional clinical information was required in order to support benefit/risk evaluation of the 10 mg/ml syrup.

2.4.2. Pharmacokinetics

Lacosamide is an active substance available on the market as 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets and a 10 mg/ml solution for injection. This line extension application concerns a lower strength of the syrup, i.e. 10 mg/ml. No pharmacokinetic studies have been submitted in support of this application and a biowaiver is proposed by the applicant.

A brief summary of the pharmacokinetic properties (relevant to this assessment) for lacosamide is provided below based on information in section 5.2 of the SmPC.

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. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised. The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%. The elimination half-life of the unchanged drug 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 CHMP concluded that lacosamide is uncomplicated from a pharmacokinetic point of view, with complete oral bioavailability, no food effect, dose-proportional and time independent pharmacokinetics and low intra- and inter-subject variability.

In the original dossier, study SP657 was included, showing bioequivalence between lacosamide tablets and 10 mg/ml syrup. The statistical results from this study are depicted below:

Table 1. Statistical results following single-dose administration of 200 mg LCM as syrup or tablet – Study SP657

Parameter	Ratio "lacosamide as syrup"/"lacosamide as tablet"	
	Estimate	90% confidence interval
$AUC_{(0-tz)}$	0.9859	(0.9691, 1.0030)
C_{max}	0.9769	(0.9173, 1.0404)

The CHMP noted that the composition of this syrup is not the same as the 10 mg/ml syrup under review. However, based on the uncomplicated pharmacokinetic characteristics of lacosamide and pharmaceutical considerations, the CHMP considered that a biowaiver was acceptable.

2.4.3. Pharmacodynamics

No new pharmacodynamic data were submitted in support of this line extension application. The pharmacodynamic properties of lacosamide were characterised in the originally submitted dossier, and hence the CHMP considered that the lack of new pharmacodynamic data was acceptable for this application.

2.4.4. Discussion on clinical pharmacology

Based on the uncomplicated pharmacokinetic characteristics of lacosamide (e.g. complete oral bioavailability, no food effect and dose-proportional pharmacokinetics) and pharmaceutical considerations, the CHMP considered that a biowaiver was acceptable.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered that a biowaiver was acceptable from a pharmacokinetic point of view and no questions were raised.

2.5. Clinical efficacy

No new studies on clinical efficacy have been submitted. The CHMP considered this to be acceptable.

2.6. Clinical safety

No new studies on clinical safety have been submitted. The CHMP considered this to be acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted an updated risk management plan.

Table 1. Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Important identified risks		
Cardiac AEs that may be potentially associated with PR interval prolongation and sodium channel modulation	Enhanced and routine pharmacovigilance Post-Authorization Safety Study SP942 to evaluate the long-term safety and tolerability of Vimpat® as add-on therapy in uncontrolled epilepsy patients with partial-onset seizures	SPC Section 4.3 Contraindication for known second- or third-degree atrioventricular (AV) block. SPC Section 4.4 Information on cardiac rhythm and conduction with lacosamide. Caution in patients with known conduction problems or severe cardiac disease and when treating elderly patients as they may be at an increased risk of cardiac disorders. Awareness of symptoms associated with second-degree or higher AV block (eg, slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (eg, palpitations, rapid or irregular pulse, shortness of breath) and that patients should be counseled to seek medical advice should any of these symptoms occur. SPC Section 4.5 Caution in patients treated with medicinal products known to be

		associated with PR prolongation and in patients treated with class I antiarrhythmic drugs. SPC Section 4.8 Information that adverse reactions associated with PR interval prolongation (eg, atrioventricular block, syncope, bradycardia) may occur. Atrioventricular block and bradycardia are uncommon ADRs. Atrial fibrillation and atrial flutter are proposed uncommon ADRs. SPC Section 5.3 Information on cardiac effects of intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure. In dogs and Cynomolgus monkeys, at 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
Suicidality as an antiepileptic product	Routine pharmacovigilance Post-Authorization Safety Study SP942 to evaluate the long-term safety and tolerability of Vimpat® as add-on therapy in uncontrolled epilepsy patients with partial-onset seizures	SPC Section 4.4 Advice that treatment with antiepileptic drugs has been associated with suicidal ideation and behaviour and that patients should be monitored. SPC Section 4.8 (proposed) Suicide attempt and suicidal ideation are uncommon ADRs.
Dizziness	Routine pharmacovigilance	SPC Section 4.4 Advice that treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. SPC Section 4.7 Information that VIMPAT may have a minor to moderate influence on the ability to drive and use machines. Advice not to drive a car or to operate other potentially hazardous machinery until patients are familiar with the effects of VIMPAT. SPC Section 4.8 Information that the most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness. Dizziness is a very common ADR.
Important potential risks		

Potential for hepatotoxicity	Routine pharmacovigilance	SPC Section 4.8 (proposed) Liver function test abnormal is an uncommon ADR. Information about abnormalities in liver function tests that were observed in controlled trials. SPC Section 5.3 Information on mild reversible liver changes observed in rats starting at about 3 times the clinical exposure after repeated dosing.
Potential for worsening of seizures	Routine pharmacovigilance	NA
Potential for abuse as a CNS-active product	Routine pharmacovigilance Post-Authorization Safety Study SP942 to evaluate the long-term safety and tolerability of Vimpat® as add-on therapy in uncontrolled epilepsy patients with partial-onset seizures	SPC Section 4.8 (proposed) Euphoric mood is an uncommon ADR
Important missing information		
Pregnant or lactating women	Routine pharmacovigilance Pregnancy registry	SPC Section 4.6 Information that there are no adequate data from the use of lacosamide in pregnant women. The potential risk for humans is unknown. Lacosamide should not be used during pregnancy unless clearly necessary. Information that it is unknown whether lacosamide is excreted in human breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with LACOSAMIDE. SPC Section 5.3 Information that no teratogenic effects but embryotoxicity at maternal toxic doses was observed in preclinical studies.
Pediatric patients	Routine pharmacovigilance	SPC Section 4.2 VIMPAT is not recommended for use in children and adolescents below the age of 16 as there is no data on safety and efficacy in these age groups.

The CHMP, having considered the data submitted, was of the opinion that the below ongoing pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Non-interventional, post-authorisation safety study SP492 to evaluate the long-term safety and tolerability of Vimpat® (lacosamide) as add-on therapy in epilepsy patients with partial-onset seizures that are uncontrolled on current therapy.	31/12/2012

No additional risk minimisation activities were required beyond those included in the product information.

2.8. 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 15 mg/ml syrup. The bridging report submitted by the applicant was found to be acceptable by the CHMP.

2.9. Changes to the product information

Summary of product characteristics, labelling and package leaflet

The MAH took the opportunity to update the product information according to the last QRD template, version 8.

3. Benefit-Risk Balance

Discussion on the benefit-risk balance

Overall the CHMP concluded the addition of the 10 mg/ml Vimpat syrup to the currently approved tablets will provide a suitable dosage form for patients with difficulties in swallowing tablets and will avoid the risk of precipitation resulting from the former 15 mg/ml syrup strength. The CHMP considered that the benefit/risk of lacosamide has not been adversely affected by the data presented in this extension application. Therefore, the risk/benefit profile of lacosamide continues to be favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vimpat 10 mg/ml syrup in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA.

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

Not applicable

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

Not applicable.