European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Vimpat

International Nonproprietary Name: lacosamide

Procedure No. EMEA/H/C/000863

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant UCB Pharma S.A. (previously Schwarz Pharma AG) submitted on 2 May 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Vimpat, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 18 October 2006.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier 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).

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
A new application was filed in the following countries: USA (28 September 2007).
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tomas P Salmonson
Co-Rapporteur: Giuseppe Nisticó

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 2 May 2007.
- The procedure started on 23 May 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 August 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 August 2007.
- During the meeting on 17-20 September 2007, 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 September 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 07 April 2008.
- During the CHMP meeting on 21-24 April 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of outstanding issues on 22 May 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 11 June 2008.
- During the meeting on 23-26 June 2008, 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 on 26 June 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 26 June 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The proposed indication for Vimpat (lacosamide) is adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older.

Lacosamide was synthesized as a member of a family of functionalized amino acids, more specifically, analogues of the endogenous amino acid and NMDA-receptor modulator D-serine.
The mechanism of action of lacosamide has to be considered still not fully elucidated. However, a dual mode of action is hypothesised: it selectively enhances slow inactivation of voltage-gated sodium channels (VGSC) and interacts with collapsin response mediator protein-2 (CRMP-2), a protein mainly expressed in the central nervous system (CNS) and involved in neuronal differentiation and axonal outgrowth.
Lacosamide showed an antiepileptic activity in different rodent seizure models for generalized and complex partial-onset seizures and status epilepticus.

Epilepsy which is defined by the recurrence of spontaneous/unprovoked seizures – i.e. seizures not provoked by systemic, metabolic or toxic disorders – constitutes a vast ensemble of very diverse clinical situations which differ by age of onset, type of seizures, aetiological background, resulting handicap, prognosis and response to treatment. More than 50 million adults and children are estimated to suffer from epilepsy world-wide. The two highest peaks of incidence are in children and in the elderly population (above 65 years). Prevalence estimates of epilepsy in the total population varies from 4 to 8 per 10000 subjects. The classification of epileptic seizures is based on clinical manifestation. The 3 main types are generalized, partial-onset (which may become secondarily generalized), and unclassified. Partial-onset epilepsies, associated with a local cerebral lesion, are the most frequent, representing approximately 60% of cases. Generalized epilepsies represent approximately 30% of cases. In the remaining 10% of seizures, the classification is uncertain.
Although some forms of epilepsy may benefit from surgical treatment and others may not require any treatment at all, most patients with epilepsy require chronic pharmacological therapy. In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS). The new AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and pharmacokinetics. However, more than 30% of patients still have inadequate seizure control or experience significant adverse drug effects on currently available AEDs. Therefore, there is still a need for AEDs with improved effectiveness and tolerability.

2.2 Quality aspects

Introduction

Vimpat application comprises three different pharmaceutical formulations:

- film-coated tablets containing 50, 100, 150 and 200 mg of lacosamide as active substance,
- oral solution containing 15 mg/ml of lacosamide as active substance,
- solution for infusion containing 10 mg/ml of lacosamide as active substance,

The ingredients of the film-coated tablets are: microcrystalline cellulose, crospovidone, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate (vegetable origin), silicified microcrystalline cellulose (Prosolv HD 90) and purified water.
The film-coated tablets are packaged in PVC/PVDC blisters sealed with aluminium foils.

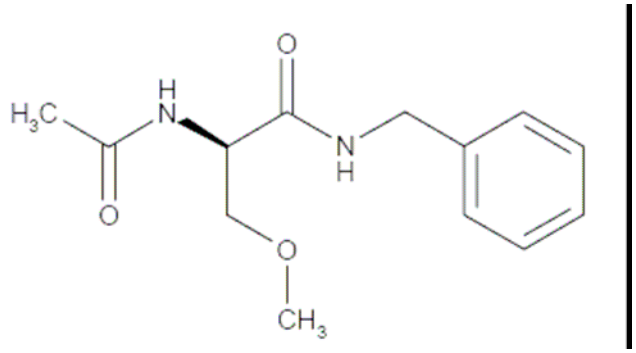
The oral solution contains the following ingredients: glycerol, carboxymethylcellulose, sorbitol (liquid crystallizing), macrogol 4000, sodium chloride, anhydrous citric acid, acesulfam potassium, sodium propyl parahydroxybenzoate, sodium methyl parahydroxybenzoate, purified water, strawberry flavours and masking flavours.

The oral solution is packed in glass type III, or PET, bottles with childproof and tamper-evident PP cap. For dosing purposes a 15 mL polypropylene measuring cup is provided.

Finally, the solution for infusion contains sodium chloride, diluted (10%) hydrochloric acid and water for injections. The solution for infusion is packaged in type I glass vials closed with a latex-free chlorobutyl rubber stopper coated with a fluoropolymer on the lower side.

Active Substance

INN Name: Lacosamide
Chemical name: (R)-2-Acetamido-N-benzyl-3-methoxypropionamide (IUPAC)
Structural formula:



Molecular formula: C13H18N2O3
Relative molecular mass: 250.30
Lacosamide is a white to light yellow non-hygroscopic powder sparingly soluble in aqueous solvents at both 25°C and 37°C and it may be classified as a Biopharmaceutics Classification System (BCS) class 1 drug substance. Its chemical name is (R)-2-acetamido-N-benzyl-3-methoxypropionamide.
Four crystalline modifications and one amorphous form of lacosamide have been identified but only crystalline polymorphs 1 and 2 are routinely formed in the synthesis processes.
The R-configuration constitutes the active substance which is validated as enantiomerically pure.

- Manufacture

The commercial synthesis process comprises five steps, which are followed by recrystallization. The manufacturers use two slightly different synthesis processes but the chemical bond forming reactions are the same.
Stereospecificity is ensured by the control of the starting material D-serine (this configuration is maintained during synthesis) and control of the drug substance; the HPLC procedure used for chiral procedure has been validated.
The polymorphic forms were characterised.
The crystalline modifications 1 and 2 are routinely formed in the synthesis processes, and only these forms are present in active substance batches; this is controlled from the IR spectra.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory. Batch analysis data produced with the proposed synthetic routes provided show that the active substance can be manufactured reproducibly.

- Specification

The active substance specifications includes tests for appearance, identity (IR spectrum and HPLC) melting point, water contents, heavy metals, sulphated ash/residue on ignition, residual solvents (GC), related substances (HPLC), chiral purity (HPLC), specific optical rotation, assay for lacosamide (HPLC) microbiological purity, bacterial endotoxins (turbidimetric kinetic method). The specifications

reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitabily described. The validation studies of all methods are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

The results comply with the specifications, and show good uniformity from batch to batch.

Batches of lacosamide that have been used in the manufacture of lacosamide solution for infusion were tested for microbiological purity and endotoxins.

- Stability

Stability studies were conducted according to ICH conditions. The long term data from lacosamide batches stored at 25°C/60% RH do not show any change in appearance, melting point, water content, chromatographic purity, chiral purity or assay. All results remain within the specification over the tested period of up to 48 months. Also, under intermediate and accelerated conditions no changes have occurred up to 2 years of storage.

Forced degradation studies (heat and humidity stress, acid or alkaline conditions, oxidizing conditions and photostability stress) were performed to determine the stability of Lacosamide in solid state and in solution under various stress conditions. Lacosamide analyzed by HPLC revealed that lacosamide is very stable under most tested conditions. There is no significant racemisation under normal conditions. The drug substance is not sensitive to oxidation or light. A remarkable degradation was only observed in solution under strong acidic or alkaline conditions.

An acceptable post-approval protocol and stability commitment has been provided. The stability data presented support the proposed re-test period with no special storage requirements.

Medicinal Product

The drug products of this application comprise immediate release film-coated tablets containing 50, 100, 150 or 200 mg of lacosamide, a syrup containing 15 mg /ml of the active substance and also an isotonic solution for infusion containing 10 mg/ml of lacosamide.

Film-coated tablets

- Pharmaceutical Development

The properties of lacosamide suggested that a tablet manufacturing process based upon wet granulation might be suitable (high solubility and high permeability but low flowability).
The tablet formulations used in clinical trials comprise white 50 and 100 mg tablets. During clinical development it became clear that higher dosage strengths than those used in the clinical trials were needed and the range of six strengths was developed. A dose proportional formulation was chosen, the advantage being that all strengths could be manufactured from one granulation.

To improve flow characteristics of lacosamide, a granulation with microcrystalline cellulose and low substituted hydroxypropyl cellulose was selected using a binder solution consisting of hydroxypropyl cellulose dissolved in water. According to studies conducted it appears that the particle size of lacosamide has no effect on processing or the tablet dissolution behaviour.

The manufacturing process has been sufficiently described and critical aspects taken into consideration are the high amount of active substance in granulate and tablets, the granulation drying process and the compression speed and force during tabletting.

All excipients are commonly used in this type of product and are compendial substances: microcrystalline cellulose (filler), low substituted hydroxypropyl cellulose (solid binder), hydroxypropyl cellulose (binder in the granulation liquid), silicified microcrystalline cellulose (for improving flow properties of the blend), crospovidone (disintegrant) and magnesium stearate

(lubricant). Silicified microcrystalline cellulose (Prosolv HD 90) is composed of the compendial components microcrystalline cellulose and colloidal silicon dioxide. Non-functional ready-to-use commercial film-coating agents are used to improve the appearance of the tablets and to facilitate swallowing; each dosage is coated with different colours

None of the materials used in the synthesis of lacosamide drug substance and excipients used in the film-coated tablets are of animal or human origin and therefore there is no risk of TSE contamination.

The lacosamide film-coated tablets are packaged in PVC/PVDC-aluminium blisters.
The components of the composite film material and the aluminium foil comply with current EU guidelines.
No interaction between the tablets and the chosen immediate packaging material, PVC/PCDC/Al blisters, has been observed during stability testing.
There are no significant effects of polymorphism on dissolution / bioavailability, therefore it is not necessary to control it. Similarly, particle size of Lacosamide has no effect on dissolution of the product.

- Manufacture of the Product

The lacosamide tablets are manufactured by a conventional wet granulation process, fluid bed drying, compression and film-coating. The granulate is common for all strengths. Narrative descriptions and flow charts valid for all strengths of tablet have been provided. The equipment used in the different steps has been indicated. The same manufacturing process is used at the two manufacturing sites.

The manufacture of the product is considered as standard. Therefore a process validation plan for production scale batches has been provided and the applicant plans to complete the process validation before marketing of the product. The six strengths of tablets being dose proportional, the process validation will be performed according to a bracketing design what is considered as acceptable.

- Product Specification

The product specifications include tests by validated methods for appearance, identity tests of lacosamide (HPLC, UV) impurities (HPLC, single and total) water content (KF), dissolution (HPLC), assay for lacosamide (HPLC), uniformity of dosage unit (PhEur) and microbiological purity (PhEur).

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Control of impurities has been sufficiently justified and the applicant has committed to tighten the total impurities shelf life limits.
The batch analysis data shows that the film-coated tablets can be manufactured reproducibly according to the agreed finished product specification.

- Stability of the Product

Three supportive batches of white film-coated tablets (clinical trial formulation), twelve primary stability batches of white film-coated tablets and six coloured primary stability batches were subjected to long term and accelerated stability studies according to ICH Q1A. According to ICH Q1D, for the white film-coated tablets a bracketing design was applied.
By testing one batch of each manufacturing site per strength, both sites were covered.
All batches were packaged in PVC/PVDC/Alu-blister.

The testing includes appearance, chromatographic purity, water content, dissolution and assay (95.0 – 105.0%). Microbiological purity is tested at release and at the end of stability testing.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are accepted.

Oral solution

- Pharmaceutical Development

The syrup was developed to provide a dosage form for patients with difficulties in swallowing tablets.

Because the drug substance is dissolved during the manufacture of the oral solution, the particle size of lacosamide is not a relevant parameter to the performance of the finished product.

The excipients were chosen in order to provide an acceptable tasting and stable syrup. For this purpose, the syrup contains taste modifying excipients, solubilizer / thickener, antimicrobial preservatives as well as purified water.
The excipients used are acesulfame potassium, carboxymethylcellulose sodium, anhydrous citric acid, glycerol, macrogol 4000, sodium chloride, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, liquid sorbitol and purified water which are tested according to the corresponding monographs of the PhEur, and also strawberry flavour and masking flavour which are tested according to in-house specifications.
No excipients are used which are of ruminant or human origin. Compatibility of the active substance with the excipients was proven by stability testing of the complete formulation. Satisfactory stability is ensured by a preservative system with sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate.

However, the toxicological information available regarding propyl parahydroxybenzoate showed some inadequacies and uncertainties. Detection of effects on sex hormones and the male reproductive organs in juvenile rats led to concluded recently that no Acceptable Daily Intake can be recommended for propyl paraben because of the lack of a clear NOAEL[1]. Although this concerns only one study and the human relevance of the adverse effects in juvenile rats is unknown (but cannot be excluded), the intake of propyl paraben when using lacosamide oral solution with the proposed formulation (0.20 mg/mL) cannot be considered as safe. Therefore, the CHMP requested the applicant to initiate a development program to remove the preservative propyl parahydroxy benzoate sodium from the formulation of the lacosamide syrup. The applicant committed to submit in an agreed time frame the necessary regulatory application as a post-approval Follow-Up measure in order to register the reformulated syrup.

The finished product is packaged in glass or polyethylene terephthalate (PET) bottles. The bottles are equipped with white tamper-evident polypropylene (PP) caps. The glass complies with the requirements of PhEur 3.2.1 Glass containers for pharmaceutical use, type III. The polyethylene terephthalate resin complies with the European requirements and also with the PhEur requirements.

For dosing purposes a 15 ml CE marked polypropylene measuring cup is provided.

- Manufacture of the Product

The manufacturing process is considered standard for this pharmaceutical form. The manufacturing process include mixing steps of active substances and excipients followed by filtration and filling in bottles and closing.

No critical process parameters were identified. However, a number of them were controlled to ensure that the process will consistently produce a product meeting its pre-determined specifications and quality attributes.

[1] Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to para hydroxybenzoates. The EFSA Journal (2004)83

Since the manufacturing process is considered standard, no validation data has been provided and the process validation on three consecutive oral solution production scale batches is to be completed prior marketing.

- Product Specification

The product specifications include tests by validated methods for appearance, identity tests of lacosamide (HPLC, UV) impurities (HPLC, single and total) water content (KF), dissolution (HPLC), assay for lacosamide (HPLC), uniformity of dosage unit (PhEur) and microbiological purity (PhEur).

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Control of impurities has been sufficiently justified and the applicant has committed to tighten the total impurities shelf life limits.

Adequate release and shelf-life specifications are validated for the drug product and include for example 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 preservatives (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 analysis data are presented for the four primary stability batches and one batch used in the bioequivalence study. All batches in the respective packages complied with the proposed specifications.

- Stability of the Product

Stability studies have been performed on four production batches of lacosamide 15mg/mL syrup under ICH conditions. Bottle-cap combinations with improved design were proposed for market launch and confirmatory stability study are now being carried out on three primary batches. Currently, 12 months data are available at long term conditions (25°C/60% RH), intermediate (30°C/65% RH,) and accelerated (40°C/75% RH) storage conditions. Intermediate and accelerated studies have been finalised.

All results complied with the proposed specifications. This is also true for the results from accelerated storage of all batches but exposure of lacosamide solutions for infusion formulation to high temperatures has resulted in the formation of particles during the development phase of the infusion.

Although the packaging material used in the stability studies is not exactly the same as intended for marketing, they are sufficiently similar to be considered as fully representative for the package intended for marketing. Also, storage of inverted bottles, studies at 5°C and thermal cycling studies between -20°C and 40°C/75% RH have been carried out. An in-use study has also been performed.

The following tests are performed during the stability studies: appearance, odour, colour, clarity, pH, chromatographic purity, lacosamide assay (HPLC), preservatives assay and microbiological purity (PhEur). Adequate microbial preservation has been demonstrated throughout the shelflife.

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.

Solution for infusion

- Pharmaceutical Development

Lacosamide isotonic solution for infusion 10 mg/mL has been developed as an emergency medication when oral administration is temporarily not feasible.

The applicant has demonstrated that there is no formation of the (S)-enantiomer during manufacture or upon storage.

Terminal sterilisation by autoclave generates visible particles in the solution. In order to avoid the formation of visible particles, a number of formulations taking into account the pH, and the concentration of the active substance were prepared during development and a sterilisation filtration process was chosen for the marketing presentation.

The solution for infusion contains sodium chloride as tonicity agent, dilute hydrochloric acid for pH adjustment and water for injections as diluent. All of them are compendial and very common ingredients for this pharmaceutical form. No excipients are used which are of ruminant or human origin.

The solution for infusion is packaged in clear colourless type I glass vials according to PhEur and closed with a latex-free chlorobutyl rubber stopper coated with a fluoropolymer on the lower.

- Manufacture of the Product

Lacosamide solution for infusion 10 mg/mL is manufactured by preparing an aqueous solution of lacosamide, sodium chloride for tonicity adjustment and diluted hydrochloric acid for pH-adjustment to the target pH. Afterwards, this solution is sterile filtered and filled into vials under aseptic conditions.
The manufacturing process has been well described, critical steps have been identified and adequate process controls are applied. The solution is tested for bioburden before sterilization by filtration. The integrity of the container closure system has been demonstrated. The manufacturing process has been satisfactorily validated with emphasis on the compounding, sterile filtration and filling steps. Results from successful media fills have been provided.

- Product Specification

The specification for lacosamide solution for infusion includes tests for appearance, clarity (PhEur), colour (PhEur), extractable volume (PhEur), osmolality (PhEur), identity of lacosamide (HPLC, UV), identity of chloride and sodium, pH (PhEur), particulate matter (PhEur), chromatographic purity, assay of lacosamide (HPLC), sterility (PhEur) and bacterial endotoxins (PhEur). The analytical methods have been validated according to ICH guidelines, where necessary.

One specified degradation product is included in the specification; the shelf-life limit is toxicologically qualified.

Batch analysis data have been presented for clinical trial batches as well as the primary stability and validation batches. All batches complied with the proposed specifications.

- Stability of the Product

Long term, intermediate and accelerated stability data for two supportive and four primary stability batches of lacosamide solution for infusion packaged in the marketing package have been provided.

One of the primary batches is stored both in an up-right and inverted position and two of the batches have been included in a stability study at 5°C, and one at -20°C.

The accelerated (6 months) and intermediate (12 months) studies have been completed, and up to 24 months of long term data for the primary stability batches have been provided. For one of the supportive batches 36 months of long term data are available.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are accepted

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner in the three pharmaceutical forms (film-coated tablets, oral solution and solution for infusion). 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 the clinic. Bioequivalence between the different oral forms has been demonstrated (see clinical part of this report). Since the product is an anti-epileptic, precise limits for assay of the active substance have been imposed at end of shelf life, to minimise the variability in dose for the patient.
The CHMP requested the applicant to initiate a development program to remove the preservative propyl parahydroxy benzoate sodium from the formulation of the lacosamide syrup. The applicant committed to submit in an agreed time frame the necessary regulatory application as a post-approval Follow-Up measure in order to register the reformulated syrup.
At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.3 Non-clinical aspects

The nonclinical development program of lacosamide for chronic use by oral and intravenous administration was conducted in accordance with the ICH guideline ICH M3 (R1).
All pivotal safety pharmacology and toxicology studies, including the determination of plasma concentrations of lacosamide, were carried out in conformance with Good Laboratory Practice (GLP) standards as claimed by the applicant.

Pharmacology

- Primary pharmacodynamics

From the results of *in vivo/in vitro* studies, two possible mechanisms of action have been suggested for lacosamide:

1. Binding of the active R-enantiomer of lacosamide to the collapsin response mediator protein-2 (CRMP-2), which has been shown to be involved in neuronal differentiation, polarization, and axonal outgrowth induced by neurotrophic factors such as brain derived neurotrophic factor. Lacosamide was demonstrated to attenuate nerve growth factor-induced axonal growth but not basal neural outgrowth.
2. Selective enhancement of sodium channel slow inactivation, without effects on fast inactivation. This effect can result in normalization of activation thresholds and a reduced pathophysiological hyperresponsiveness thereby effectively controlling neuronal hyperexcitability

Lacosamide was tested in different models of chemoconvulsant-induced seizures, and did not block generalized tonic-clonic convulsions induced by the GABAA-receptor antagonist bicuculline, and the chloride-channel blocker picrotoxin. Lacosamide was also ineffective against clonic seizures induced by the sc bolus injection of the chemoconvulsant pentylenetetrazole in rats and mice. Lacosamide at 20 and 50 mg/kg ip, completely antagonized tonic convulsions, and at 50 mg/kg also partially antagonized clonic convulsions induced by NMDA in male mice.
Lacosamide, but not the S-enantiomer nor its main metabolite SPM 12809, protected both mice and rats against seizures induced by maximal electroconvulsive shock (MES), indicating that lacosamide is

effective in preventing seizure spread. Lacosamide was also tested in a model of electrostimulated limbic seizures in the mouse which demonstrated protection against clonic seizures and stereotyped behaviour.
Lacosamide was effective in the hippocampal kindling model, thought to reproduce complex partial seizure. Lacosamide was also equally effective in this model when compared with reference antiepileptic drugs (phenytoin, carbamazepine, valproic acid, and ethosuximide) administered at maximally effective doses.
Lacosamide was also active in models of status epilepticus. Limbic seizures induced by self-sustaining status epilepticus in rats stopped within 15 min after lacosamide injection and did not recur over the next 24 h.
A neuroprotective ability was observed as histological examination of brain sections (dorsal hippocampus) collected 72 h after status epilepticus which revealed significantly less damage in lacosamide-treated rats compared with control animals.
Lacosamide was without effect in a genetic animal model for absence epilepsy.

- Secondary pharmacodynamics

An extensive number of secondary pharmacodynamic studies demonstrated antinoceptive effects in animal models of neuropathic pain, acute and chronic inflammatory pain, in cancer and musculoskeletal pain but not in visceral pain. A neuroprotective effect of lacosamide was seen *in vitro* at concentrations (≥ 1 µmol/L). A significant reduction (25 mg/kg ip) in infarct volume was seen in one animal model for neuroprotection *in vivo*, while another study on infarct volume was negative. An indication of effect against tardive dyskinesia was demonstrated in mice at a dose of 30 mg/kg ip. Furthermore, lacosamide at doses at and above 1 mg/kg was effective in an animal model for essential tremor. Slight effect was noted in some animal models for psychiatric disorders.

- Safety pharmacology programme

Safety pharmacology studies were performed in mice, rats, dogs and monkeys or in established *in vitro* models, on the central nervous, cardiovascular and respiratory systems in accordance with relevant recommendations and guidelines ICH S7A (2000) and ICH S7B (2005). In addition effects on renal and gastrointestinal autonomic nervous systems have been evaluated. Animal studies on potential abuse liability were conducted in accordance with the EMEA "Guideline on the non-clinical investigation of the dependence potential of medicinal products" (EMEA/CHMP/SWP/94227/2004) (see Toxicology part, Dependence).

Central nervous system
Early neuropharmacological screening test in male mice: no effects were found (10mg/kg ip).
Motor coordination (rotarod test) in male mice and rats: lacosamide dose-dependently impaired rotarod performance in mice (8, 16 and 32 mg/kg ip) and in rats (32, 64 and 128 mg/kg), with significant effects at 32 mg/kg in both species.
Series of Irwin tests (as part of efficacy screening) as in rats and mice ip or oral doses: lacosamide induced qualitatively similar effects in both species and both routes of application, including dose-dependent sedation, rolling gait, decreased muscle tone and at higher doses ataxia tremor and hypothermia. Decreased respiration was seen in rats after 32 mg/kg ip or 256 mg/kg po. Straub tail was observed after ip application of 32 mg/kg in the mouse and 64 mg/kg in the rat. Convulsions occurred in the mouse at 64 mg/kg ip.
GLP modified Irwin test in rats: lacosamide had no statistically significant neurobehavioral neurotoxic or neurovegetative effects (3 and 10 mg/kg), induced a statistically significant decrease in spontaneous locomotor activity, delayed passivity to finger approach and in body and abdominal tones (25 mg/kg), effects more marked and long-lasting effects at doses of 50 and 75 mg/kg. Moreover, at a dose of 75 mg/kg, a statistically significant decrease in grip strength was observed at 60 or 240 minutes post-dosing. Lacosamide had no effect on body temperature at any of the doses tested. The NOEL was determined to be 10mg/kg po.
Neurotoxic effects of lacosamide were assessed in two rat studies: no neuronal vacuolization or cell death were observed at 4 h or 72h following single ip administration of 10 or 50 mg/kg lacosamide, while MK-801 treatment resulted in the expected neuronal vacuolization and necrosis.

Cardiovascular and autonomic nervous system

In vitro studies on Purkinje fibers, human SCN5A channel, guinea pig ventricular myocytes and *in vivo* dog study with lacosamide cumulative application have been performed in full compliance to GLP principles.

In *in vitro* studies, lacosamide reduced action potential duration in cardiac tissue and sodium current in isolated cells, starting at concentrations which shouldn't be achieved in the clinic, ie 50 to 60 µmol/L (ca. 12-15µg/mL), corresponding to 300mg bid. Effects on sodium current were dependent on membrane potential, with higher inhibition at more depolarized potentials. A positive use/frequency dependence was observed in recombinant human sodium channels, whereas effects on action potentials in Purkinje fibers did not display a frequency dependence under the experimental conditions used. The investigations on cardiac ion currents suggest that inhibition of sodium currents, presumably via enhancement of slow inactivation, is responsible for the changes in action potential shape in Purkinje fibers.

Pivotal cardiovascular *in vivo* studies in the dog and monkey

In a GLP study in anesthetized instrumented dogs intravenous lacosamide induced short lasting hypotensive effects which appeared at the time of maximal drug plasma levels (T_{max}), i.e. 2 to 5 minutes after iv application. The lacosamide plasma levels eliciting this effect (11.3 to 22.6 µg/mL) started at plasma levels found in humans after twice daily dosing of 300 mg (14.5 ± 1.7 µg/mL), which was the initially proposed Maximum Recommended Human Dose (MRHD). During the assessment, the applicant changed the dose recommendations due to the unfavourable benefit/risk profile of the 600mg/day dose. The MRHD was therefore reduced from 600 mg/day to 400 mg/day (see Clinical part). The small, but statistically significant reduction of blood pressure (7-8% at initial proposed MRHD-equivalent plasma concentration of 600 mg/day) after lacosamide application is most likely due to a cardiodepressant action and not an effect on blood vessels, because no significant change in peripheral resistance was observed. At all doses tested (ie 2-12 mg/kg) a slight, but statistically significant increase of heart rate (3-7%) was determined. The cardiodepressant activity was characterized mainly by reduced contractility as indicated by decreases in systolic left ventricular pressure (LVP) and dP/dt and reduced cardiac output which amounted to 7-9%, 12-17% and 6-7%, respectively, at 600mg/day -equivalent plasma concentrations. These effects were accompanied by an increase in PR interval and QRS complex duration of 4-6% and 8-11%, respectively, at 600mg/day -equivalent drug concentrations.

These changes were dose-dependent and consistently found in all haemodynamic studies of lacosamide in anesthetized, instrumented dogs. Atrial conduction was affected at lower doses than ventricular conduction. Higher doses (15-45 mg/kg iv) of lacosamide were only studied in a few anesthetized, instrumented dogs. In these early studies more severe conduction disturbances like AV block, AV dissociation and nodal rhythm were observed. AV dissociations were accompanied by marked reductions in blood pressure and cardiac output. The results from these studies indicate that the effects of lacosamide on the electrocardiogram (ECG) are dose-dependent. However, due to the small number of animals no clear dose-effect relationship can be established.

Effects on cardiac conduction and haemodynamic parameters similar to those in dogs were also observed in monkeys at doses of 30 mg/kg iv and higher.

Due to the low number of animals tested (n=3) no dose-effect relationship can be established, but to summarize the study in monkeys, lacosamide induced a dose-dependent transient decrease of blood pressure and disturbances of atrial and ventricular conduction. However, the degree of severity varied considerably between the animals.

Negative dromotropic as well as negative inotropic effects have already been described for a number of different sodium channel modulators. Cardiodepressant effects of carbamazepine and phenytoin in anesthetized dogs have been reported (Steiner et al (1970, Smith and Lomas, 1978 and Gupta et al, 1967).

- Pharmacodynamic drug interactions

Lacosamide showed synergistic effects with diazepam in the rat cobalt/homocysteine model of

status epilepticus. The ED_{50} of lacosamide was reduced by 91% in the presence of diazepam.

Lacosamide was also examined in the rat late phase formalin test for sustained pain for pharmacodynamic interactions with common analgesics. The results suggest the following interactions:
- Additive effects were observed between lacosamide 20 mg/kg and gabapentin 50 and 100 mg/kg.
- Synergistic effects were observed between lacosamide 10 mg/kg and duloxetine 8 mg/kg (stronger analgesic effect of the combination than the sum of the effects of each substance alone).
- No clear interaction was observed between lacosamide and naproxen.
- Synergistic effects were observed between lacosamide 10 and 20 mg/kg and morphine 2 and 4 mg/kg (stronger analgesic effect of the combination than the sum of the effects of each substance alone).
- Weak synergistic effects were observed between lacosamide 10 mg/kg and memantine 8 mg/kg and between lacosamide 20 mg/kg and memantine 4 mg/kg (stronger analgesic effect of the combination than the sum of the effects of each substance alone).

Upon request of the CHMP the applicant presented also data on the interaction of lacosamide with other AEDs. Results from one large study using the 6 Hz model of psychomotor seizures and the rotarod test for motor impairment indicated that there are particularly strong synergistic effects of lacosamide in combination with either levetiracetam or carbamazepine. Additive to synergistic effects were observed for lacosamide in combination with lamotrigine, gabapentin and topiramate. Purely additive effects were seen with valproate and phenytoin. No synergistic or additive effects were seen for the motor side effect where the pharmacodynamic interactions were infra-additive.

Pharmacokinetics

Absorption, distribution, metabolism and excretion of lacosamide were studied in mice (CD-1), rats (Sprague Dawley) and dogs (Beagle) and in rabbits (New Zealand White). Data were obtained both from pharmacokinetic and toxicokinetic studies, using oral, intravenous and intraperitoneal dosing, various dose levels and duration of treatment. Plasma concentrations of the major human O-desmethyl metabolite (SPM 12809), were determined in mice, rats and dogs and the desacetyl metabolite (SPM 6912), was quantified in mouse plasma.

- Absorption

In mice, the absorption of lacosamide was rapid following a single oral administration of 20 mg/kg. Blood levels of radioactivity mimicked those in plasma. Pharmacokinetic parameters were similar in males and females. After a single, oral and intraperitoneal, and repeated oral administrations, C_{max} increased approximately or slightly less than proportionallly to the dose.
In rats, the absorption of lacosamide was rapid after a single oral administration of 10 mg/kg, the mean bioavailability was 94%. Blood levels of radioactivity mimicked those in plasma. Peak plasma and blood levels and T_{max} were similar in male and female rats and systemic exposure tended to be slightly higher in females.
Following a single oral administration of 40 mg/kg a secondary elevation of plasma levels was seen, suggesting the possibility of entero-hepatic recirculation of radiolabelled moieties.
After repeated dose administration, systemic exposure in male and female rats was similar and saturation was observed at high dose levels. In both genders, the systemic exposure was slightly less than dose proportionate. There was no difference in pharmacokinetic parameters following single or multiple oral administration. The $t_{1/2}$ was approximately 1.3 hours in rat.
In pregnant rats, dosed orally once daily on gestation days 7 to 17 with up to 300 mg/kg/day, plasma concentrations were slightly lower than that in non-pregnant female rats in the 3-month study after single dose.
In juvenile rats, plasma concentrations of lacosamide were in general higher than in adults and C_{max} was observed at later time points.
In pregnant rabbits, following oral dosing from days 6 to 18 of gestation with up to 50 mg/kg, the lacosamide plasma concentration-time profiles were essentially the same as on day 1 of dosing.

In dogs, the absorption of lacosamide was rapid following a single oral administration of 10 mg/kg, with a bioavailability ranging from 71 to 97% in different studies. The blood concentrations were similar to those in the plasma. After repeated dose administration, exposure to lacosamide was similar in both genders and increased approximately in proportion to the dose. The $t_{1/2}$ was short, at about 2 hours. No accumulation of lacosamide in plasma was observed.

- Distribution

Tissue distribution following single oral administration was investigated by qualitative whole body autoradiography and tissue sampling. *In vitro* binding to plasma proteins and blood cell partitioning were also determined.

In mice, the tissue distribution was extensive following a single oral administration of 20 mg/kg [^{14}C]-lacosamide, up to 72 hours post dose. Highest concentrations were seen in stomach mucosa and kidney, later in the organs of metabolism and excretion and the lachrymal glands. In general, concentrations in tissues were below systemic exposure up to 4 hours post dose and were greater than systemic exposure from 8 hours onwards. At 72 hours post dose concentrations had fallen to between 0.3% and 11% of their peak values. Tissue concentrations were in general similar in male and female mice. No specific binding to any tissue was seen.
In albino rats, tissue distribution was rapid after an oral or intravenous single administration of 10 mg/kg [^{14}C]-lacosamide. The distribution was uniform and wide after both routes of administration, with no organ showing excessive concentrations or preferential uptake. There was no significant retention of radioactivity at 48 hours post dose by any organ. The distribution was similar between genders, and, excluding gastrointestinal tract and content, the same general distribution pattern was observed following oral and intravenous administration.
In male pigmented rats, following single oral administration of 10 mg/kg [^{14}C]-lacosamide, the highest concentrations were reached in the coagulating gland, followed by kidney cortex and medulla, uveal tract and liver. Radioactivity was detected in central nervous system, with very few regional differences in the distribution of radioactivity in the brain and with concentrations about half that in plasma. At the final sampling time (35 days post dose), most tissues (except periosteum, periodontal membrane, skin and lens) contained radioactivity at levels below the limit of quantification. Following a single intravenous administration of 10 mg/kg [^{14}C]-lacosamide radioactivity was highest in kidney cortex and medulla and the esophageal wall, coagulating gland, uveal tract, prostate and small intestine mucosa.
In pregnant/lactating rats, on day 18 of gestation, or to dams on day 10 post partum, after a single oral dose of 10 mg/kg [^{14}C]-lacosamide, radioactivity was widely distributed into maternal tissues. [^{14}C]-lacosamide-derived radioactivity readily crossed the placental barrier with concentrations in the foetal tissues comparable with the corresponding tissues in the dam. Suckling neonates were exposed to radioactivity with a distribution similar to that of maternal tissues.
In dogs, following a single oral administration of 10 mg/kg [^{14}C]-lacosamide, radioactivity was widely distributed throughout all tissues and about half of the tissues contained concentrations in excess of those found in blood; highest concentrations were detected in the epididymis, kidneys, gall bladder and liver.

The CHMP asked the applicant a justification for not conducting repeat-dose evaluations in the distribution studies, and to discuss the risk of accumulation in the tissues where lacosamide was still present after 35 days post dose.
The applicant argued that the low levels of radioactivity detected in tissues of pigmented rats at 35 days post-dose were similar to those in other non-pigmented tissues, indicating that no significant melanin binding occurs. It is reasonable to assume that the conducted single dose tissue distribution studies provide an adequate assessment of tissue distribution in the rat since similar pharmacokinetic parameters regarding absorption and excretion were obtained in male rats receiving a single radioactive dose or six non-radiolabelled doses followed by a single radioactive dose of lacosamide at 10 mg/kg (4 MBq/kg). In addition, no lacosamide related changes were seen in the repeat-dose toxicity studies in the ophthalmological examinations or in the histopathological examinations of the eye and skin. Further, no effects on skin or eyes have been seen clinically.

Protein binding
The binding of [^{14}C]-lacosamide to plasma proteins was determined *in vitro* by equilibrium dialysis of mouse, rat, dog and human plasma in the concentration range of 1.5 to 60 µg/mL [^{14}C]-lacosamide. The protein binding of [^{14}C]-lacosamide was low; 6.2, 5.1 and 6.1% in mouse, rat and human, respectively. No concentration dependent effects were observed. In the dog, protein binding was 16.5% and showed some degree of saturation. Mean blood cell partitioning of [^{14}C]-lacosamide was 49, 44, 47 and 54% in mouse, rat, dog and human, respectively.

- Metabolism

In vitro metabolism
Liver microsomes from rat, dog, cynomolgus monkey and human were incubated with lacosamide at 100 µmol/L (25 µg/mL). Lacosamide was slowly metabolized with concomitant formation of both phenolic and desmethyl metabolites in the animal hepatocytes. The metabolite profiles from rat, dog or monkey showed no significant species differences. Slow biotransformation of lacosamide was exhibited in human liver microsomes.

Suspension cultures of hepatocytes isolated from the livers of male mouse, rat, dog, human and female rabbit were incubated with [^{14}C]-lacosamide at 10 µmol/L (2.5 µg/mL). Metabolic turnover rated human < rabbit < dog < rat < mouse. After 4 hours incubation, on average 55% (mouse), 22% (rat), 7% (rabbit), 15% (dog) and 4% (human) of lacosamide had been metabolized. SPM 12809 was common to all species. Deacetylation occurred in mouse and human, hydroxylation in rat, rabbit and dog. There was no evidence for Phase II metabolites in any species after treatment with either ß-glucuronidase/aryl sulphatase or sulphatase-free ß-glucuronidase.

Further, metabolism of lacosamide was investigated in liver and kidney microsomes obtained from rat and human, in liver and kidney microsomal supernatant from rat, in human plasma and in microsomes obtained from baculovirus infected insect cells transfected with human cytochrome P450 2C19 cDNA at a concentration of 100 µmol/L (25 µg/mL). Recombinant CYP2C19 microsomes were incubated at 10 µmol/L. Also, the influence of flavin monooxygenase enzymes was investigated.
In the *in vitro* rat models, a total of 4 significant metabolites (> 1%) were observed. SPM 12809 and SPM 12817 accounted for up to 4.9 and 2.7%, respectively, of the total radioactivity. Traces of SPM 6912 were also identified. Two unknown polar metabolites accounted for up to 1.6 and 1.5% in the liver supernatant samples. One of the unknown polar metabolites (up to 1.5%) was also found in the kidney microsomal supernatant. The formation of both unknown polar metabolites was independent from cytochrome P450 activity.
In the *in vitro* human models, a total of 3 significant metabolites were observed. SPM 12809 and SPM 6912 accounted for up to 2.5 and 1.4%, respectively, in liver microsomes. Using recombinant human CYP2C19 microsomes, 2 significant metabolites were observed: SPM 12809 (up to 6.9%) and a polar metabolite (up to 7.7%).
There was no evidence that flavin monooxygenase is involved in the biotransformation of lacosamide.

The metabolic formation of M6, the N-carbamoyl glucuronide of the desacetyl metabolite SPM 6912, was investigated using human liver microsomes. Mainly unchanged SPM 6912 and trace amounts of M6 were identified.

In vivo metabolism
Metabolite profiles in mouse, rat and dog plasma, urine and faeces were compared. Samples were obtained following single oral dosing of [^{14}C]-lacosamide at 20, 40 and 10 mg/kg to male and female mice, rats and dogs, respectively and single intravenous dose of 10 mg/kg to rats and dogs.

In a repeat-dose study Sprague Dawley rats were dosed orally with 10 mg/kg/day lacosamide. Plasma, urine and faeces samples were analyzed. In plasma SPM 12809 accounted up to 36% (6 hours post dose) and SPM 12816 up to 6%. Percent radioactivity of unchanged lacosamide ranged from 80 to 89% and from 50 to 67% at 1.5 and 6 hours post dose, respectively.
In urine two major metabolites were SPM 12809 and SPM 12817 in both genders. Similar data were obtained in both genders and after single and repeated administration.

Faeces samples contained 3 to 7% of the administered dose. Due to the low radioactivity of the samples, mouse faeces were not used for metabolite identification. In rat and dog faeces the predominant component was SPM 12817 with concentrations ranging from 1.5% (rat) to 2.2% of the dose (dog). Three further principal components, accounting for 1.1, 0.5, 0.1% in rats and 0.9, 1.0, 0.5% in dogs, were identified as unchanged lacosamide, SPM 12809 and a dihydroxy metabolite, respectively. The rat faeces samples showed an additional main component, SPM 12816 which accounted for 0.6 and 0.3% of the dose in male and female rats, respectively.
In healthy male human subjects the major compounds excreted into urine after both oral and intravenous administration of 100 mg [^{14}C]-lacosamide were unchanged lacosamide (approximately 40% of the administered dose) and SPM 12809. Smaller amounts (<10%) of SPM 6912 and its N-carbamoyl glucuronide were also found in urine. Minor peaks (<6%) were the O-desmethyl hydroxy (meta and para) and the p-hydroxy metabolites.

Systemic exposure of SPM 12809 in plasma
Plasma concentrations of SPM 12809 were determined in mice, rats and dogs following repeated oral administration of lacosamide. Peak plasma concentrations and areas under the curve of lacosamide were generally higher than those of SPM 12809. No major differences in systemic exposure to SPM 12809 were observed between species, dose levels and genders. In human plasma, the relative exposure to SPM 12809 in percentage of the lacosamide exposure was 12% in terms of $C_{max,ss}$ and 15% in terms $AUC_{0\text{-}12\ h,ss}$ (200 mg lacosamide bid for 6 days, SP640).

Systemic exposure of SPM 6912 in plasma
Plasma concentrations of SPM 6912 were determined in mice after oral administration of lacosamide for up to 14 days. The major component circulating in plasma was lacosamide followed by SPM 12809, 22% to 87% of the parent compound. SPM 6912 represented 3% to 10% of the parent compound.

Racemization
Lacosamide is a chiral compound and the potential bioconversion to its S-enantiomer was investigated in rat plasma and dog urine. No bioconversion was seen in either species. In addition, stereospecific analysis of urine samples showed that there is no enantiomeric interconversion in humans.

N-carbamoyl glucuronide of SPM 6912
The N-carbamoyl-glucuronide (M6) of SPM 6912 was identified as a minor metabolite (<10% of the administered dose) in human urine, but was not found in plasma. Rat urine samples from the carcinogenicity study and dog urine samples derived from the pharmacokinetic study LPT 15654/02, were investigated for M6. Traces of M6 were detected in 1 out of 5 rats and in 1 of 5 dogs.

Enzyme induction
The potential for lacosamide to induce the cytochrome P450 isoforms 1A2 and 3A4 was investigated in cryopreserved human hepatocytes at 50 µmol/L and 500 µmol/L lacosamide. A slight induction of CYP3A4 in one of the two examined donors was seen in the presence of acetonitrile as vehicle.
In a second *in vitro* induction study the cytochrome P450 isoforms 1A2, 2B6, 2C9, 2C19 and 3A4 were examined. In one donor, enzyme activities of CYP3A4 after treatment at 500 µmol/L, was increased.
In male rats treated orally with vehicle, 3.9 or 100 mg/kg lacosamide for 7 days, no increase in overall cytochrome P450 concentration, CYP1A or CYP2B activity was seen.

- Excretion

In mice, excretion of [^{14}C]-lacosamide in urine and faeces was investigated following a single oral administration at a dose level of 20 mg/kg by gavage. Excretion of radioactivity was rapid with >84% of the dose recovered within 48 hours. Radioactivity was mainly excreted in the urine.
In rats, excretion of [^{14}C]-lacosamide was investigated after an administration of either 10 mg/kg or 40 mg/kg orally or intravenously at 10 mg/kg. Radioactivity was determined in urine, faeces, expired gases and carcasses. Elimination was principally via urine with >75% of the dose recovered within 24 hours. Total recovery ranged from 91% to 100%. Routes and rates of excretion of radioactivity were

similar in males and females, after oral and intravenous dosing and after single and repeated oral dosing.
In dog, excretion of [^{14}C]-lacosamide in urine and faeces was investigated following single oral (gavage) or single intravenous administration at 10 mg/kg.
In humans, receiving either a single oral administration or intravenous infusion of 100 mg [^{14}C]-lacosamide (Study SP619), about 95% of the administered radioactivity was recovered in urine and less than 0.5% in faeces after 7 days, indicating that renal excretion is the main pathway for the elimination of lacosamide in man.

Excretion in rat milk
After a single oral dose of 10 mg/kg [^{14}C]-lacosamide to female rats at 10 days post parturition, radioactivity was excreted into the milk. Concentrations of radioactivity peaked at 2 hours post dose in milk. Mean milk over plasma ratios increased from 0.7:1 at 30 minutes to 2.5:1 at 8 hours and then decreased to 0.9:1 at 24 hours after dose administration.

Toxicology
All pivotal toxicity studies were performed according to GLP standards.

- Single dose toxicity

NOAEL was 31.6 mg/kg in both mice and rats after oral dosing. Single dose toxicity was also evaluated in dogs; the only dose was 15 mg/kg by oral gavage. Observed exaggerated pharmacodynamic effects on the central nervous system were dose dependent and dose limiting. Lacosamide concentrations in female mice, in the high dose groups and after oral dosing was 31.8 µg/mL at 316 mg/kg, and 124 µg/mL at 464 mg/kg. When comparing allometrically corrected non-lethal doses, the multiple to human dose, 12 mg/kg (600 mg daily and a patient weighing 50 kg, gives 12 mg/kg), was approximately 2 in mice, and no margin at all in rats and dogs.

- Repeat dose toxicity (with toxicokinetics)

The animal species tested in the pharmacokinetic studies, mice, rats and dogs, are suitable species for the toxicity studies. However, the central nervous system effects were dose limiting in all tested species and the margins to human exposure are low or non-existent.

In mice, lacosamide was administered up to 270 mg/kg for 13 weeks. Central nervous system effects started at 60 mg/kg, and no other signs of toxicity were seen. No target organ was identified in the mouse, possibly due to dose-limiting central effects. The NOAEL was considered to be 60 mg/kg, even though slight central nervous system related effects were obvious already at this dose level. At NOAEL the C_{max} was 29 µg/ml and AUC_{0-24h} was 97 µg·h/mL. The initially proposed MRHD of 600 mg/day was reduced to 400mg/day due to the unfavourable clinical safety profile at 600 mg/day. Therefore, the margin over human maximum exposure (200 mg bid) is 2.7 for C_{max} and none (1.0) for AUC.

In rats, lacosamide was administered up to 180 mg/kg by oral gavage for 26 weeks (4 weeks recovery) and up to 50 mg/kg by intravenous (bolus) administration for 2 weeks. In the oral studies, the central nervous system related dose limiting effects were seen at 180 mg/kg and above, and after intravenous administration at 50 mg/kg. The female rats were more affected by the central nervous system effects than the males.
The liver was also a target organ in rats; at approximately 100 mg/kg, increases in serum alkaline phosphatase, cholesterol, triglycerides and alanine aminostransferase were seen, along with increases in liver weights, in both males and females. These increases were of moderate character. A light and electron microscopic examination of female rat livers at 300 mg/kg after 13 weeks, revealed mild to moderate hypertrophy of the centrilobular and peripheral hepatocytes, with an increase of the rough reticulum and mitochondria. Some of the mitochondria had atypical morphology and were classified as mega mitochondria. It has been shown that lacosamide is metabolised *in vitro* by CYP2C19 forming SPM 12809, both in rat and human. Further, in the carcinogenicity study, increases in ALT and liver weights were seen after week 13 at mid and high doses, however, at week 52 and onwards

the increases were smaller and not statistically significant. No effects on the liver (enzymes, weights or histopathology) were seen in the liver in any of the studies in mice and dogs, at maximum doses tested. In addition, no adverse effects on the liver function have been recorded in the clinical studies. Taken together, it is agreed that the effects of the liver seen in the rat are indicative of increased enzyme production, i.e. a physiological adaptive process, and are not of clinical relevance.
A slight diuretic effect was seen in the 13-week and 26-week oral studies, an increase in urine output with concomitant dilution of urine solutes (lower nitrogen, creatinine, sodium and potassium) and an increase in some haematology parameters (mean cell volume, segmented neutrophils and mean cell haemoglobin) was noticed. All these changes were of a mild magnitude and no diuretic effects have been observed in the clinic. In the oral 6-month study, at NOAEL (90 mg/kg), C_{max} was 26 µg/ml and AUC_{∞} was 299 µg·h/mL, which leaves a margin over human maximum exposure (200 mg bid) of 2.4 for C_{max} and 3.0 for AUC.

In dogs, lacosamide was administered orally up to 20/25 mg/kg for 12 months (4 weeks recovery) orally, and up to 16 mg/kg for 2 weeks by intravenously (bolus) administration. In the dog, the heart was the target organ. A slight trend to increased heart rate was seen after oral administration in the 30-day, 3-month and 12-month studies. These increases were of moderate magnitude, statistically significant only in male dogs at mid dose (12 mg/kg) in the 3 month study. A moderate decrease in arterial systolic blood pressure was recorded in the 12-month study at 10 mg/kg and above in female dogs only. However, apart from one female in the 2-week intravenous study, who suffered a second degree AV block at Day 13 (at 16 mg/kg), no changes were seen in ECG parameters in any dog study. Pharmacology studies in anesthetized, instrumented dogs showed that lacosamide caused reduction of blood pressure (7-8%), increase of heart rate (3-7%) due to reduced contractility, and a short lasting hypotensive effect at 11.3-22.6 µg/mL, which is however above the C_{max} range obtained after maximum recommended clinical dosing. These effects were accompanied by an increase in PR interval and QRS complex duration of 4-6% and 8-11%, respectively. At higher doses (15-45 mg/kg) more severe conduction disturbances like AV block, AV dissociation and nodal rhythm were observed. The C_{max} obtained in the highest dose group in the 3-month, 12-month oral and 2-week intravenous study ranged between 20-30 µg/mL, levels where heart effects would have been more pronounced. It is reasonable that this might be due to the fact that ECG assessments were made after T_{max} and that awake dogs are less sensitive to the cardiodepressant effects than anesthetized open-chest dogs. However, further preclinical testing would in any case not add any relevant information, since these effects have also been seen in the clinic.
Central nervous system related effects, decreased food consumption and body weight parameters were seen at approximately 20 mg/kg and above. In the intravenous study, a slight diuretic effect was seen, however no diuretic effect was seen in the dog after oral administration. No local toxicity, after intravenous administration, was noted.
In the 12-month study, at NOAEL (10 mg/kg), C_{max} was 14 µg/ml and AUC_{∞} was 71 µg·h/mL for males and 55 µg·h/mL for females. In the intravenous study, at NOAEL (8 mg/kg), C_{max} was 13 µg/ml and AUC_{∞} was 48 µg·h/mL.

- Genotoxicity

Lacosamide was tested according to relevant guidelines.
In the two Ames tests, no mutagenic effect in any of the tested strains, irrespective of metabolic activation, was seen. However, equivocal (without metabolic activation) and positive (with metabolic activation with rat liver S9 mix) results were observed in the *in vitro* mouse lymphoma assay. The weak increase in small colonies suggests a clastogenic effect. The positive response was seen at a high concentration, 8 mM, albeit not cytotoxic concentrations. Even though the positive effects in the mouse lymphoma assay were seen at high concentrations, and the other studies included in the standard genotoxicity battery were negative, the CHMP requested the applicant to submit a weight-of-evidence analysis of these positive effects. In response the applicant put forward convincing arguments regarding the interpretation of the mouse lymphoma assay, that this assay should be regarded as negative in absence of S9 and equivocal in presence of S9. Any equivocal evidence of genotoxicity above 10 mM in the presence of S9 is considered likely to be an artefact due to excessively high test concentrations.

Lacosamide was negative in the two *in vivo* tests, mouse micronucleus test and unscheduled DNA synthesis (UDS) in rat. The clinical signs were dose limiting in the *in vivo* studies. No separate toxicokinetics were available for the micronucleus study. The C_{max} after 200 mg/kg lacosamide given intraperitoneally was 241.2 µg/mL and the $AUC_{(0-6h)}$ was 768 µg·h/mL, yielding margins over human maximum exposure (200 mg bid) of 22.1 and 7.7 for C_{max} and AUC, respectively. For the UDS study, based on C_{max} values, the margin over human maximum exposure (200 mg bid) was 3.5.
In addition, a structure alert search using DEREK was performed by the assessors, and no structure alert was identified.

- Carcinogenicity

2-year carcinogenicity studies were conducted in mice and rats, with dosing by oral gavage up to 180 mg/kg (mice) and 160 mg/kg (males rats) and 160/180/200 mg/kg (female rats). A complete histopathology was carried out in both studies and no lacosamide or vehicle-related neoplastic or non-neoplastic lesions were observed in either species.

In the mice, the survival rate varied between 34-68%, no difference between males and females were noted (mid dose males having a slighter decreased survival rate, 34%). At the end of the 2-year dosing period, body weight was reduced by -10.6% and -1.8% in the high dose males and females, respectively.
In 2 out of 12 control samples lacosamide was detected just above the LoQ, 1.0 ng/mL. It is agreed by the Assessor that these contamination of samples are of an order of magnitude that does not affect data quality and the integrity of the study.
At the highest dose of 180 mg/kg mean exposure to lacosamide over all sampling days, as C_{max}, was approximately 71 and 51 µg/mL for males and females, respectively. Based on AUC_{last}, levels of approximately 268 and 217 µg·h/mL were reached for males and females, respectively. The resulting exposure margins over human maximum exposure (200 mg bid) are 6.5/4.7 (males/females) based on C_{max} and 2.7/2.2 (males/females) based on AUC.
In the rats, due to subsiding toxicity in high dose females, the dose was increased twice, in week 51 to 180 mg/kg, and in week 74 to 200 mg/kg. Clinical signs (abdominal position, clonic convulsion and reduced motility) were noted up to week 29, then only few rats on few occasions showed any clinical signs. After raising the dose in the females at week 51, half of the rats showed abdominal position, but only that week. After the second raise in dose at week 74, again 50% of the females showed reduced motility/abdominal position up to week 96.
Increases in ALT was seen in week 13, however, at week 52 and onwards the increases were smaller and not statistically significant. In addition, increases in absolute and relative liver weights were seen. Liver effects were seen in the repeated-dose toxicity studies in rat, and the findings in the carcinogenicity studies confirm the liver being the target organ in rats. These effects are indicative of increased enzyme production, i.e. a physiological adaptive process.
The survival rates ranged between 54-74% and no difference between male or female rats was noted. At the end of the 104-week dosing period, body weight was reduced by -7.9% in males and -2.5% in females.
In 6 out of 42 control samples lacosamide was detected just above the LoQ, 1.0 ng/mL. These contaminations of samples are of an order of magnitude that does not affect data quality and the integrity of the study.
Mean exposure to lacosamide over gender at the highest dose of 160 mg/kg on the first sampling day (in test week 26), as C_{max}, was approximately 53 µg/mL. Based on AUC_{last}, levels approximately 587 µg·h/mL were reached. The resulting margins over human maximum exposure (200 mg bid) are 4.9 based on C_{max} and 5.9 based on AUC.

- Reproduction Toxicity

Fertility and early embryonic development
In rats, no adverse effects on male or female reproductive function when studying standard parameters up to 200 mg/kg were seen. NOAEL was >200 mg/kg for both males and females. At NOAEL, the margin to maximum human exposure (200 mg bid) was 3.1 based on C_{max} and 4.7 and 1.2 for males and females, respectively, based on AUC values.

Embryo-foetal development
In rats, there was no evidence on a teratogenic potential at doses up to 200 mg/kg. However, the clinical signs (starting at 70 mg/kg) in the dams were dose limiting. A decrease in food consumption and body weight (-4.7% on day 15) was seen in the high dose dams. No effects on other standard parameters were noted. NOAEL was >200 mg/kg for both males and females. At NOAEL, the margin to maximum human exposure was 2 based on C_{max} and 3 and 1 for males and females, respectively, based on AUC values.
In rabbits, there was no evidence on a teratogenic potential at doses up to 50 mg/kg. However, as in rats, the clinical signs in the dams were dose limiting. A slight decrease in food intake and body weight gain and body weight in the dams was observed. At 50 mg/kg, a slightly reduced foetal body weights were seen. There were no other effects on other standard parameters. At maternal NOAEL, 12.5 mg/kg, no margins over maximum human exposure (200 mg bid) based on C_{max} (1.2) or AUC values (0.9) were established.

Prenatal and postnatal development, including maternal function
In rats, dosed up to 200 mg/kg, the mean duration of gestation was significantly prolonged in treated groups (22.8, 22.9 and 23.0 days, respectively), compared with the control group (22.4 days). Also, an increase in numbers of stillborn pups and pup deaths in the peripartum period, and a slightly reduced live litter sizes and pup body weights were observed at a maternally toxic dose of 200 mg/kg/day. No effects were noted on the F2 generation up to weaning. The NOAEL for maternal and developmental toxicity was 70 mg/kg, for development, fertility and reproduction of F1 generation it was >200 mg/kg. At NOAEL, 70 mg/kg, the margins to maximum human exposure based on C_{max} was 2.3 and no margin for AUC values was established. At NOAEL >200 mg/kg, the margins over human maximum exposure (200 mg bid) was 3.0 based on C_{max}, and no margin based on AUC levels.

- Local tolerance

Lacosamide had no effects on haematocrit, erythrocyte morphology, haemolysis, osmolality, or precipitation/coagulation in human blood.
In rabbit, after intramuscular, paravenous and subcutaneous injections, minimal to mild inflammatory, hemorrhagic and/or necrotic intolerance reactions were seen. No effects were noted after intravenous and intra-arterial infusion. Concentration was 20 mg/mL in all administrations.
Lacosamide was non-irritating to the skin when applied to intact and abraded rabbit skin. When instilled in to rabbit eye, lacosamide caused corneal opacity, irritation of the iris and conjunctival redness and is classified as “irritating to eyes”.

- Other toxicity studies

<u>Antigenicity</u>
Lacosamide was negative for skin sensitization reactions in guinea pigs, using Magnusson/Kligman grading scale.

<u>Immunotoxicity</u>
Lacosamide did not have any immunotoxicological properties in mice with respect to an IgM and IgG response against SRBC. The resulting safety margins based on body weight and body surface area with respect to immunotoxicological effects in this study were >31.5 and >2.4, respectively (adjusted for 200 mg bid).

<u>Dependence</u>

In studies using rats for 26 weeks and dogs for 12 months with recovery, at the maximum dose, a checklist of behavioural and physical signs of drug action was employed. A post-hoc analysis of these two toxicity studies revealed no new behavioural or physical signs after cessation of dosing.

<u>Drug abuse:</u>
In order to assess the potential abuse liability of lacosamide three dedicated animal studies were performed.

1) Drug discrimination study a group of drug-naïve rats were trained to discriminate between ip injections of vehicle (physiological saline) and 10 mg/kg of lacosamide while responding under a fixed-ratio 10 schedule of food reinforcement. Consistent with the weak nature of the stimulus effects of lacosamide, the time taken to achieve discrimination with it (59.0 ± 4.2 training sessions) was longer than has been reported for establishing two-choice discrimination with the comparison substances used in the present study (Carter et al, 2004, Bartoletti et al, 2000, Mori et al, 2002).
   In the subsequent generalization testing, lacosamide itself, diazepam, morphine, phencyclidine and phenobarbital were tested for generalization to the lacosamide stimulus. When lacosamide itself was tested, the pattern of responding was best described as random, underlining the difficulty the rats had reliably to distinguish lacosamide from saline. The generalization studies with the comparison substances with known abuse and dependence liability are consistent with the weak lacosamide discriminative cue as the pattern of responding was essentially random at all doses. In conclusion, the discriminative stimulus produced by lacosamide in rats was not robust, nor clearly dose-dependent suggesting that the test substance is not likely to have subjective effects leading to abuse in man.
2) Further, lacosamide was investigated after oral (gavage) administration in the conditioned place preference test in the rat; morphine hydrochloride was used as reinforcing drug, and the vehicle was used as negative control. Contrary to morphine, lacosamide did not affect the time spent in the drug-paired compartment during the test session as compared with the vehicle control. The number of crossing was not affected.
3) Furthermore, when lacosamide was compared to cocaine and physiological saline for its ability to maintain intravenous self-administration in rats, it didn't demonstrate to maintain self-administration at all doses tested.

These results suggest that lacosamide is not likely to have positive reinforcing properties or abuse potential.

The evaluation of the dependence potential of lacosamide provided by the applicant, was considered to be not completely exhaustive. However, there were no signs of withdrawal symptoms clinically, and further preclinical studies would not add any relevant information to the overall risk/benefit of the patient.

Studies on impurities
Impurity SPM 14018, was considered qualified regarding the repeated-dose toxicity studies performed with batch KK02457.

However, it was unclear from the submitted dossier, what the actual amount of SPM 14018 was in batch PEH-A-188(2), used for the genotoxicity tests (Ames and mouse lymphoma assay). The applicant was asked to clarify what the actual amount of SPM 14018 was in the batch used for the genotoxicity tests performed, and justify the claim of a 0.3% qualification limit.
The applicant decided to tighten the acceptance limit for SPM 14018 in lacosamide drug substance to NMT 0.15% based on batch analysis data, i.e. below the ICH Q3A (R) qualification threshold.
Considering the statement of the applicant to tighten the acceptance limit for the impurity SPM 14018 and the review analysis of genotoxic data, the applicant response was accepted.

SPM 6912, a degradation product and a mouse and human (<10%) metabolite, is considered toxicologically qualified.

Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) in accordance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (CHMP/SWP/4447/00), 1 June 2006, was prepared by the Applicant. In addition to a number of studies on physico-chemical properties six studies on environmental fate and effects were performed in accordance with GLP to support the ERA.

Based on the low K_{ow}, lacosamide is not considered as potentially bioaccumulative and thus not a PBT substance, and further PBT assessment is not required.

The adsorption/desorption was investigated for four different soils and one sediment and the obtained Koc values ranged from 5 to16 mL/g. This is well below the action limit of 10 000 L/kg. The adsorption/desorption study is required in order to investigate the fate of the compound in the sewage treatment plant. Consequently, sewage sludge should have been tested. However, considering the low Koc values obtained further testing using sewage sludge is not warranted. It can be concluded that there is no concern for the soil compartment.

Lacosamide was not readily biodegradable. In accordance with the guideline (CHMP/SWP/4447/00), the fate of substances which are not readily biodegradable should be further investigated in a water sediment study (OECD 308). This was not done by the Applicant. Instead, the % partitioning into sediment was calculated to 2 % and 7 % using the obtained Koc value in an equation based on a FOCUS surface water scenario. These calculations cannot be accepted as a replacement of the OECD 308 study, which still is required. Should the partitioning into sediment, at any time point after or at 14 days, exceed 10 %, additional sediment effect studies are required. The applicant committed to submit the results of an ongoing aerobic water sediment study (OECD 308) as a post approval follow-up measure. This was considered acceptable by the CHMP.

Lacosamide was of low toxicity to aquatic organisms with chronic NOEC values for algae, *Daphnia* and fish of > 100 mg/L, 32 mg/L, and 10 mg/L, respectively. No inhibitory effect on the respiration rate of activated sludge microorganism was observed, and the 3-hour NOEC was > 1000 mg/L.

The PEC/PNEC quotients for the aquatic and sewage compartment were all well below 1 and 0.1, respectively. It can be concluded that the proposed use of lacosamide is unlikely to represent an unacceptable risk to the terrestrial and aquatic compartments. However, a final conclusion cannot be made regarding the sediment compartment.

Discussion on the non-clinical aspects

The CHMP was concerned about the possible interaction of lacosamide with other AEDs. Results presented by the applicant indicated that there are particularly strong synergistic effects of lacosamide in combination with either levetiracetam or carbamazepine. Additive to synergistic effects were observed for lacosamide in combination with lamotrigine, gabapentin and topiramate. Purely additive effects were seen with valproate and phenytoin. No synergistic or additive effects were seen for the motor side effect where the pharmacodynamic interactions were infra-additive.

The CHMP also requested clarification why no repeat-dose studies had been conducted, and to discuss the risk of accumulation in the tissues where lacosamide was still present after 35 days post dose. The data provided by the applicant indicated that no significant melanin binding occurs and therefore it was reasonable to assume that the conducted single dose tissue distribution studies provided an adequate assessment of tissue distribution in the rat. In addition, no lacosamide related changes were seen in the repeat-dose toxicity studies in the ophthalmological examinations or in the histopathological examinations of the eye and skin. Further, no effects on skin or eyes have been seen clinically.

The applicant also reassured the CHMP on the results of the *in vitro* mouse lymphoma assay, demonstrating that that this assay should be regarded as negative in absence of metabolic activation, and the equivocal results in presence of metabolic activation considered likely to be an artefact due to excessively high test concentrations.

With regard to the impurities, it was unclear from the submitted dossier, what the actual amount of SPM 14018 was used for the genotoxicity tests (Ames and mouse lymphoma assay). The applicant was asked to clarify what the actual amount of SPM 14018 was in the batch used for the genotoxicity tests performed, and justify the claim of a 0.3% qualification limit.
The applicant decided to tighten the acceptance limit for SPM 14018 in lacosamide drug substance to NMT 0.15% based on batch analysis data, i.e. below the ICH Q3A (R) qualification threshold.

Considering the statement of the applicant to tighten the acceptance limit for the impurity SPM 14018 and the review analysis of genotoxic data, the applicant response was accepted.

Lacosamide is not readily biodegradable, and the required (in accordance with the guideline CHMP/SWP/4447/00) water sediment study was not performed. The applicant committed to submit the results of an ongoing aerobic water sediment study (OECD 308) as a post approval follow-up measure. This was accepted by the CHMP.

Studies on dogs indicated a relevant effect of lacosamide on atrioventricular conduction; however further preclinical testing would not add any relevant information, since these effects have also been seen in the clinic.

2.4 Clinical aspects

Introduction

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. It has also shown effect in animal models of neuropathic pain.
The precise mechanism by which lacosamide exerts its antiepileptic and analgesic effects remains to be fully elucidated. Preclinical experiments suggest that lacosamide has a dual mode of action: *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable physiological neuronal excitability. Additionally, lacosamide binds to collapsin response mediator protein 2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system. CRMP-2 is found to be dysregulated in the brain of epileptic patients.
The phase III development program for Vimpat consists of 6 completed and 3 ongoing Phase 2/3 trials for adjunctive treatment for subjects with partial-onset seizures (using oral [tablet/capsule] formulation). A total of 1338 adult subjects with partial-onset seizures with or without secondary generalization have been treated with oral Vimpat 100mg/day to 800mg/day as adjunctive therapy. In addition to the film-coated tablets, a parenteral solution of Vimpat (10mg/mL) in sodium chloride for intravenous infusion has been developed. For administration in patients who have difficulty swallowing tablets, flavoured syrup with a concentration of Vimpat 10mg/mL or Vimpat 15mg/mL has been developed.

The proposed indication for Vimpat is adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Absorption

Lacosamide is a modified aminoacid with a fast and complete absorption. The bioavailability after oral administration approaches 100%. Three formulations are applied for: film-coated tablets 50, 100, 150 and 200mg, solution for infusion 10 mg/ml, and oral solution 15 mg/ml. Bioequivalence has been shown between clinical trial tablets and 30 or 60 minutes of oral infusion. If the infusion is administered over 15 minutes, a 20% higher mean Cmax is obtained and bioequivalence can not be shown. Bioequivalence has also been shown between the clinical trial tablet and an oral solution of a different concentration than the solution applied for marketing (10 mg/ml). The tablet intended for marketing is slightly different than the clinical trial formulation but has not been studied *in vivo*. A biowaiver from studying bioequivalence between the marketing tablet formulation and the clinical trial

formulation was granted as the formulation can be classified as BCS class I and have similar and fast dissolution at different pH *in vitro*, the drug has high permeability, apparently little intestinal transporter involvement, and the excipients in the formulation are unlikely to affect transport proteins. A biowaiver was also accepted for a bioequivalence study between the oral solutions of different concentrations. As the drug is in solution, and the solution does not contain any excipient known to affect drug absorption, this was granted.

- Distribution

Lacosamide has a low protein binding and a volume of distribution of 40-60 L.

- Elimination

The elimination half-life is 11-16 hours and clearance ca 3 l/h. The inter-individual variability is low (ca 20%). Lacosamide shows 1-compartment kinetics and the kinetics is dose and time proportional in the therapeutic range. Lacosamide is eliminated partly (30%) through renal excretion and partly by metabolism. The non-renal elimination has not been fully characterised. In the mass-balance study, 19-40% of the dose was found in urine as the inactive metabolite SPM12809. (The metabolite coeluted with another metabolite, so the figure is imprecise.) However, the formation of the metabolite is said to be catalysed by CYP2C19 but absence or inhibition of CYP2C19 only gave a 7-17% reduction of oral clearance. Thus, either the contribution of the pathway is rather small or another enzyme is contributing to the SPM12809 formation. The applicant has tried to identify the remaining metabolic pathways and enzymes responsible as catalysts, but although quite extensive investigations, no further information has been collected. The identification of dose-related compounds in plasma is borderline acceptable. Only a pooled plasma sample from all time points of a full sampling curve was studied. The rough estimation results in lacosamide contributing to 60-100% of plasma radioactivity. SPM12809 was the only metabolite found in plasma. The pharmacokinetics of SPM12809 has been investigated in several studies. The exposure of SPM12809 is usually 15% of the lacosamide exposure.

- Chirality

Lacosamide has one chiral centre and is administered in the R-form. There is no significant interconversion *in vivo*.

- Special populations

Impaired renal function gives an expected increase in lacosamide exposure (47% in severe renal impairment). The drug is eliminated by haemodialysis and an additional half morning dose should be taken after end of dialysis. A maximum dose of 250 mg (instead of 400mg) is recommended for patients with severe renal impairment and in patients with end-stage renal disease. Very high concentrations of SPM12809 were noticed in patients with severe impairment and end-stage renal disease. The exposure margin to preclinically obtained exposures is, as for the parent drug, small or non-existent. In patients with end-stage renal disease, the plasma concentrations were increased and continued to rise during the complete sampling period. Thus, AUC could not be determined. However, no pharmacological activity of the metabolite has been observed. A recommendation of caution when treating patients with end-stage renal disease is proposed in the SPC. The AUC of lacosamide was increased by 60% in moderately impaired hepatic function. However, the studied patients also had an impaired renal function and it was estimated that the increase in AUC resulting from a decrease in non-hepatic clearance was 19%. The exposure was also similar in Asians, Blacks and Whites. Elderly women had approximately 50% higher mean AUC than young men both after the first dose and at steady state, and elderly men had approximately 33% higher exposure than young men. After normalising the parameters for bodyweight, the differences were reduced (to 23% for elderly women and 26% in elderly men as compared to young men). Only a minor part of the difference is likely to be due to decreased renal function. The pharmacokinetics in children has not been studied. However, studies in this age group are planned. Weight appears to modestly influence the pharmacokinetics of lacosamide. The population PK analysis supported that women will have an increased lacosamide

exposure and indicated that decreased weight will lead to increased exposure. Combining information from the various sources, indicates that elderly females with low body weight may have increased lacosamide exposure.
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

- Pharmacokinetic interaction studies

In vitro studies indicate that CYP3A4 may both be induced and inhibited by lacosamide. The signal is not very strong but nevertheless, it may not be excluded that lacosamide can affect this enzyme activity in a moderate way. The applicant will study this in a multiple dose study with oral midazolam. A Caco-2 cell transport study indicates that there is some efflux transport. The concentration dependency of the transport has not been evaluated. The concentrations used in the study are quite high and the possibility of lacosamide to be transported by aminoacid transporters or peptide transporters such as PEPT1 may not be excluded. However, as there are no indications of relevant transporter involvement *in vivo* (high permeability, no active renal or biliary excretion), no further investigations were considered as needed. Lacosamide does not affect digoxin transport *in vivo* and the transport was not affected by the Pgp inhibitor verapamil *in vitro*. *In vivo* interaction studies showed that multiple-dose omeprazole (40 mg q.d.) increased lacosamide exposure by 19%, lacosamide slightly (9%) increased ethinylestradiol and levonogestrel exposure, did not affect the pharmacokinetics of digoxin. There was no interaction between lacosamide and metformin, valproic acid and carbamazepine. However, the interaction study with carbamazepine did not include a sufficiently long carbamazepine treatment period at the target dose for full induction to be reached. The population analysis indicated that concomitant treatment with phenytoin, phenobarbital and carbamazepine moderately decrease lacosamide exposure.

- PK/PD relationship

Lacosamide increases the PR interval. The effect is dose-dependent and a relationship between concentration and increase in PR interval has been found. There is one PK-PD analysis on efficacy which estimates that the plateau in response will be reached at higher lacosamide doses than indicated by the clinical efficacy data. However, the analysis is a rough estimation.

Pharmacodynamics

The mechanism of action for lacosamide is incompletely known but is thought to involve an enhancement of the slow inactivation of sodium channels, and possibly an interaction with collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axon outgrowth. Lacosamide has demonstrated antiepileptic activity in some 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 (for details see non-clinical section). Lacosamide has also shown effect in animal models of neuropathic pain.
Administration of lacosamide in healthy subjects showed dose-dependent mild sedation. There was no evidence for extrapyramidal effects and no significant influence on the saccadic eye movement as an indicator of possible central nervous system (CNS) effects. Phase 1 trials with ECG investigation showed that lacosamide causes a dose-related increase of the PR interval. In Study SP640, the maximum mean changes on Day 6 (steady-state) were observed at 1 hour post dose and were 6.3ms, 13.6ms, and 18.2ms in the placebo, lacosamide 400mg/day, and lacosamide 800mg/day dose groups, respectively.

Clinical efficacy

The clinical development program for orally administered Vimpat includes 7 clinical trials that evaluated efficacy of Vimpat tablets as adjunctive therapy in adult subjects with partial-onset seizures.

This includes 3 primary double-blind, placebo-controlled efficacy trials (SP667, SP754, and SP755) in 1294 adult subjects, 1 completed supporting trial (SP607), and 3 ongoing trials (SP615, SP756, and SP774) evaluating long-term efficacy. Two additional completed trials (SP586/FRC-01-201 and SP598/FRC-01-202) used a capsule formulation, however only very few patients received Vimpat in these trials and therefore they will not be commented further.
For Vimpat solution for infusion, there are 2 completed phase 2/3 trials including a total of 199 subjects for adjunctive treatment of partial-onset seizures. These trials were designed to investigate the appropriate duration of infusion for Vimpat as short-term replacement for oral Vimpat and to provide safety data for the intravenous formulation. An overview of the 9 trials evaluating efficacy of the oral formulation Vimpat is shown in Table 1, and trials of iv administered Vimpat are provided in Table 2.

Table 1. Trials evaluating efficacy of oral formulation Vimpat in adults with partial-onset seizures.

Protocol number	Trial design	LCM dose	Maximum treatment duration	Total number of subjects[a]
Primary efficacy trials				**Randomized**
SP667	Multicenter, DB, PC	200, 400, and 600mg/day	21 weeks	418[b]
SP754	Multicenter, DB, PC	400 and 600mg/day	21 weeks	405
SP755	Multicenter, DB, PC	200 and 400mg/day	18 weeks	485
Supporting efficacy trial				**Treated with LCM**
SP607	Multicenter, OL, UC	Up to 600mg/day	14 weeks	91
Long-term efficacy trials				**Treated with LCM**
SP615	Multicenter, OL, UC	Up to 800mg/day	8 years	370
SP756	Multicenter, OL, UC	Up to 800mg/day	4 years	232
SP774	Multicenter, OL, UC	Up to 800mg/day	4 years	376
Other efficacy trials				**Treated with LCM**
SP586	Multicenter, OL, UC	Up to 600mg/day	4 weeks	13
SP598	Multicenter, OL, UC	Up to 600mg/day	20 months	8

DB=double-blind; LCM=lacosamide; OL=open-label; PC=placebo-controlled; UC=uncontrolled
a These numbers do not represent unique exposures as a subject may have participated in more than 1 trial.
b Because of audit findings suggesting noncompliance with the protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

Table 2. Trials of intravenously administered Vimpat in subjects with partial-onset seizures

Trial number/clinical development phase/trial design	Number of unique exposures to iv LCM[a]	Number of subjects exposed to iv placebo	Maximum duration of treatment
SP616/Phase 2/Multicenter, double-blind, double-dummy, randomized trial to investigate safety, tolerability, and PK of iv LCM as replacement for oral LCM[b]	30-min infusion: 19 60-min infusion: 20	30-min infusion: 11 60-min infusion: 10	2 days
SP757/Phase 3/Multicenter, open-label trial to evaluate safety and tolerability of iv LCM as a replacement for oral LCM	10-min infusion: 20 15-min infusion: 100 30-min infusion: 40	NA	2-5 days
Total[c]	10-min infusion: 20 15-min infusion: 100 30-min infusion: 59 60-min infusion: 20	30-min infusion: 11 60-min infusion: 10	NA

iv=intravenous; LCM=lacosamide; min=minute; NA=not applicable; PK=pharmacokinetics

a Subjects receiving LCM in SP616 and SP757 were previously exposed to oral LCM (200 to 800mg/day) in an open-label extension trial.

b Subjects receiving iv LCM received a placebo tablet and subjects receiving iv placebo received a LCM tablet.

c Total for the 30-min infusion rate represents subjects from SP616 and SP757.

Data source: 5.3.5.1.4 EP: SP616 CTR, 5.3.5.2.7 EP: SP757 CTR

- Dose response studies and main clinical studies

The main clinical efficacy studies for the use of Vimpat as adjunctive therapy in adults with partial-onset seizures are study SP667 (conducted in the United States and Europe), study SP754 (conducted in the United States), and study SP755 (conducted in Europe and Australia). Study SP667 was designed as a dose-response trial but also served as a trial supporting the efficacy and safety of Vimpat as add-on treatment for partial onset seizures. Further details for these trials are provided in Table 3.

Table 3. Primary efficacy trials with Vimpat as adjunctive therapy in adults with partial onset seizures.

Trial number/clinical development phase/trial design	Number of subjects randomized to receive LCM[a]	Number of subjects randomized to receive placebo[a]	Maximum duration of treatment[b]
SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day)	200mg/day: 107 400mg/day: 108 600mg/day: 106	97	21 weeks
SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)	400mg/day: 204 600mg/day: 97	104	21 weeks
SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)	200mg/day: 163 400mg/day: 159	163	18 weeks
Total	200mg/day: 270 400mg/day: 471 600mg/day: 203 Total: 944	364	

LCM=lacosamide

a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

b All 3 trials had a 12-week Maintenance Phase.

Data source: 5.3.5.1.1 EP: SP667 Table 3; 5.3.5.1.2 EP: SP754 Table 2.3.1; 5.3.5.1.3 EP: SP755 Table 2.3.1

General description of the three main studies SP667, SP754 and SP755

The three main studies were similar in design with similar inclusion criteria, a 12-week maintenance phase, and subjects were allowed to back-titrate 100 mg/day at the end of the titration phase. The three trials also used doses, dosage forms and dosing schedules that were the same as the initial (including 600mg dose) proposed product label. A general description of the three main studies is provided below.

Study participants

Subjects were included if they were male or female, age 18 to 65 years in SP667 and 16 to 70 years in SP754 and SP755. Included subjects had a diagnosis of epilepsy with simple partial-onset seizures and/or complex partial-onset seizures with or without secondary generalization according to the International Classification of Epileptic Seizures (1981). Subject should have partial-onset seizures for at least the previous 2 years despite prior therapy with ≥2 AEDs. Included subjects reported ≥4 partial-onset seizures per 28 days on the average, with seizure-free period no longer than 21 days, in the 8-week period prior to entry into the baseline phase. In addition, subjects were on a stable dosage regimen of 1 to 2 (SP667) or 1 to 3 (SP754 and SP755) concomitant AEDs with or without additional

concurrent vagal nerve stimulation (VNS). The dosage of concomitant AEDs was kept constant for ≥4 weeks prior to entry into the baseline phase and throughout the trial.
Patients were excluded if they had received Vimpat in a previous trial, if they had a history of chronic alcohol or drug abuse with the previous 2 years, if they had a known history of severe anaphylactic reactions or serious blood dyscrasias. Subjects with a history of primary generalised seizures, subjects with seizures that were uncountable due to clustering, and subjects with a progressive structural lesion in the CNS or a progressive encephalopathy were also excluded.

Treatment
In each trial, subjects were enrolled and entered into an 8-week Baseline Phase. Subjects were randomized if they reported ≥4 partial-onset seizures per 28 days on the average, with seizure-free period no longer than 21 days during the baseline phase. After randomization, the subjects began double-blind treatment: a 4- (SP755) or 6-week (SP667 and SP754) forced titration up to the respective randomized dose of Vimpat (200, 400, or 600mg/day) or placebo. In all 3 trials, active treatment was initiated at 100mg/day and increased in weekly increments of 100mg/day to the target dose. A 1-step back-titration of Vimpat 100mg/day or placebo was allowed in the case of intolerable adverse events at the end of the titration phase. Then followed a 12-week maintenance phase on the achieved randomized (or back-titrated) dose, and either a 2-week transition phase or a 2- (SP755) or 3-week (SP667 and SP754) taper phase. The 2-week transition phase was required for subjects who completed the maintenance phase and who chose to enrol in an open-label extension trial of Vimpat. The 2- to 3-week taper phase was required for subjects who chose not to enrol in the open-label extension trial of Vimpat or who did not complete the titration or maintenance Phases.

Outcomes/endpoints
Primary efficacy variables
Two primary variables were defined in each of these trials.
For the European regulatory agencies, the primary variable was the proportion of responders (at least 50% reduction in seizure frequency from Baseline to the Maintenance Phase), *with the primary variable for the FDA as a secondary variable*.
For the FDA, the primary variable was the change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase, whereas response to treatment ≥50 % was a secondary variable.

Secondary efficacy variables
Secondary variables included:
• Change in partial seizure frequency per 28 days from Baseline to Maintenance Phase (for European Union regulatory agencies)
• *Response to treatment of ≥50% from Baseline to Maintenance Phase (for FDA)*
• Response to treatment of ≥50% from Baseline to Treatment Phase (ie, Titration + Maintenance Phases)
• Proportion of subjects experiencing an increase (≥25%) in partial seizure frequency from Baseline to Maintenance Phase and from Baseline to Treatment Phase (ie, Titration + Maintenance Phases)
• Proportion of subjects experiencing rebound seizure (defined as an increase in partial seizure frequency ≥100% from Baseline to Taper Phase) (SP754 and SP755 only)
• Change in partial seizure frequency per 28 days from Baseline to Maintenance Phase and from Baseline to Treatment Phase (ie, Titration + Maintenance Phases) by seizure type
• Proportion of seizure-free days during the Maintenance Phase for subjects who entered the Maintenance Phase
• Proportion of subjects who achieved "seizure-free status" (yes/no) during the Maintenance Phase for subjects who completed the Maintenance Phase
• Clinical Global Impression of Change at the end of the Titration (SP667 only) and Maintenance Phases
• Change in Seizure Severity Scale ratings from Baseline to the end of the Maintenance Phase (SP754 and SP755 only)
• Change in Quality of Life in Epilepsy - 31 assessment from Baseline to the end of the Titration (SP667 only) and Maintenance Phases
• Health Outcomes Assessment (SP754 and SP755 only)

Main results for the pivotal clinical studies

In general, the demographic characteristics were evenly distributed between the groups in all three main trials. The use of concomitant antiepileptic drugs was also in general evenly distributed between the groups. Only few patients above 65 years were included. Subjects included in the three main efficacy trials had difficult to control epilepsy, and their seizures were not adequately controlled despite treatment with 1 to 3 concomitant antiepileptic drugs. Nearly half of them had tried 7 or more marketed antiepileptic drugs. The mean duration of epilepsy was 23.7 years in these 3 trials and the median baseline seizure frequency was 9.9 to 16.5 seizures per 28 days across all treatment groups.

Study SP667
This study, which also served as a dose-response trial, compared the effect of three dose levels of Vimpat with placebo. A total of 542 subjects were screened from which a total of 497 subjects were enrolled and 421 were randomized (98 to placebo, 107 to Vimpat 200mg/day, 109 to Vimpat 400mg/day, and 107 to Vimpat 600mg/day). Data on subject demographics are provided in table 4.

Table 4. Summary of subject demographics for the treatment arms in Study SP667. Population: Safety set

Parameter	Placebo N=97	SPM 927 200mg/day N=107	SPM 927 400mg/day N=108	SPM 927 600mg/day N=106
Age (years)				
Mean (SD)	38.9 (11.11)	39.9 (11.71)	41.2 (11.61)	39.4 (10.53)
Min, Max	19, 66	18, 65	18, 68	18, 64
Weight (kg)				
Mean (SD)	79.5 (20.90)	74.5 (17.16)	77.5 (18.63)	75.7 (19.40)
Min, Max	45.0, 155.4	45.0, 129.3	43.0, 142.0	42.2, 143.8
Gender				
Male n (%)	47 (48)	46 (43)	53 (49)	45 (42)
Female n (%)	50 (52)	61 (57)	55 (51)	61 (58)
Ethnic origin				
Caucasian n (%)	88 (91)	98 (92)	100 (93)	101 (95)
Black n (%)	6 (6)	4 (4)	5 (5)	2 (2)
Asian n (%)	0 (0)	2 (2)	0 (0)	0 (0)
Other n (%)	3 (3)	3 (3)	3 (3)	3 (3)

Data Source: Table 10; SD=standard deviation

321 subjects completed the 12-week Maintenance Phase. A total of 415 subjects had at least 1 post-Baseline efficacy assessment and were considered part of the Full Analysis Set (FAS). A total of 312 (75%) subjects completed the trial, and 103 (25%) subjects discontinued early from the trial. The most common reason for discontinuation was adverse events (72 subjects overall; 5 [5%], 16 [15%], 19 [18%], and 32 [30%] in the placebo, Vimpat 200mg/day, Vimpat 400mg/day, and Vimpat 600mg/day groups, respectively).

The results for the primary efficacy parameter responder rate in the full analysis set population are shown in table 5.

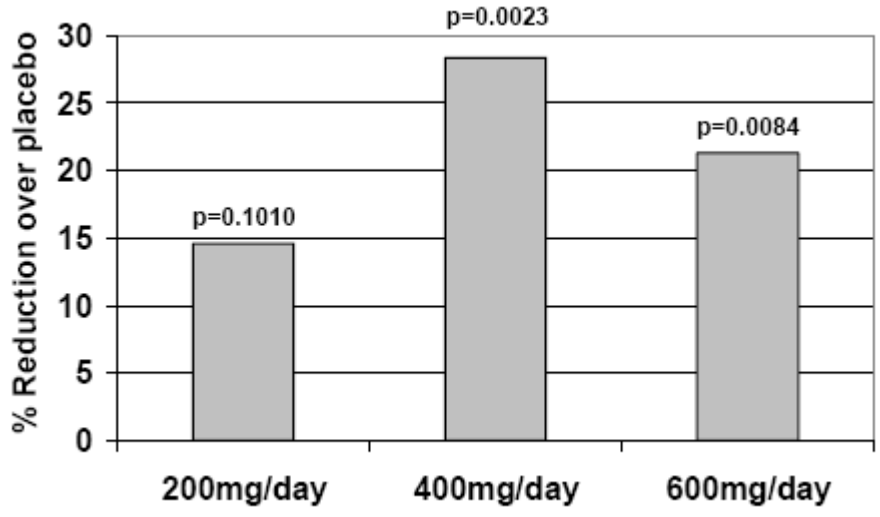
Table 5. Study SP667. Proportion of patients who were 50 % responders at maintenance endpoint. Full analysis set.

Treatment	50% Responder	Unadjusted difference compared with placebo	Odds ratio	P-value for odds ratio
Placebo	22%	NA	NA	NA
600mg/day	38%	16.2%	2.2	0.0141*
400mg/day	41%	19.2%	2.5	0.0038**
200mg/day	33%	10.8%	1.7	0.0899

**Significant at the 0.01 level; *Significant at the 0.05 level
NA=not applicable
Data source: Table 46 and Table 70

In this study, the responder rate in the placebo group was relatively high, 22 %. Both the higher doses 400 mg and 600 mg/day were statistically significantly superior to placebo, whereas the 200 mg/day dose was not. There was no dose-response relationship between the 400 and 600 mg/day doses with regard to the primary efficacy endpoints. This was true also for some of the secondary endpoints including seizure-free status and seizure reduction with at least 75 %. The change in frequency over placebo at endpoint (secondary endpoint) is shown in figure1.

Fig. 1. Percent reduction of seizure frequency over placebo at maintenance endpoint (Full analysis set).



Study SP754
This study had a similar design as the preceding study, SP667. Study SP754 was multi-centre, double-blind, randomised and placebo-controlled and investigated the efficacy and safety of Vimpat 400 mg/day, 600 mg/day and placebo as adjunctive therapy in subjects with partial seizures with or without secondary generalisation. A total of 542 subjects were screened for the trial, and 497 patients were enrolled. Of these, 421 were randomised and received at least one dose of trial medication. Data on subject demographics are shown in table 6.

Table 6. Summary of demographics for study SP754

Parameter	Placebo N=104	LCM 400mg/day N=204	LCM 600mg/day N=97	Total N=405
Age (years)				
Mean (SD)	38.1 (11.96)	39.1 (12.37)	36.8 (11.76)	38.3 (12.13)
Min, Max	16.0-61.0	17.0-71.0	16.0-69.0	16.0-71.0
Age (years) n (%)				
<65	104 (100.0)	197 (96.6)	96 (99.0)	397 (98.0)
≥65	0	7 (3.4)	1 (1.0)	8 (2.0)
Gender n (%)				
Male	49 (47.1)	104 (51.1)	47 (48.5)	200 (49.4)
Female	55 (52.9)	200 (49.0)	50 (51.5)	205 (50.6)
Weight (kg)				
Mean (SD)	75.4 (18.48)	83.9 (21.65)	80.8 (21.26)	81.0 (21.03)
Min, Max	43.1-163.3	38.6-187.8	39.9-143.3	38.6-187.8
BMI (kg/m^2)				
Mean (SD)	26.4 (5.50)	29.3 (7.52)	28.2 (7.13)	28.3 (7.05)
Race n (%)				
White	84 (80.8)	166 (81.4)	80 (82.5)	330 (81.5)
Black	12 (11.5)	18 (8.8)	8 (8.2)	38 (9.4)
Asian	1 (1.0)	3 (1.5)	1 (1.0)	5 (1.2)
Other	7 (6.7)	17 (8.3)	8 (8.2)	32 (7.9)

BMI=body mass index; LCM=lacosamide; Max=maximum; Min=minimum; SD=standard deviation

Data source: Table 3.1.1

The results for 50 % responder rate for the Full Analysis Set population are presented in table 7. The difference vs. placebo was statistically significant for both doses.

Table 7. Study SP 754. Proportion of patients (%) with 50 % responder rate. Full Analysis Set

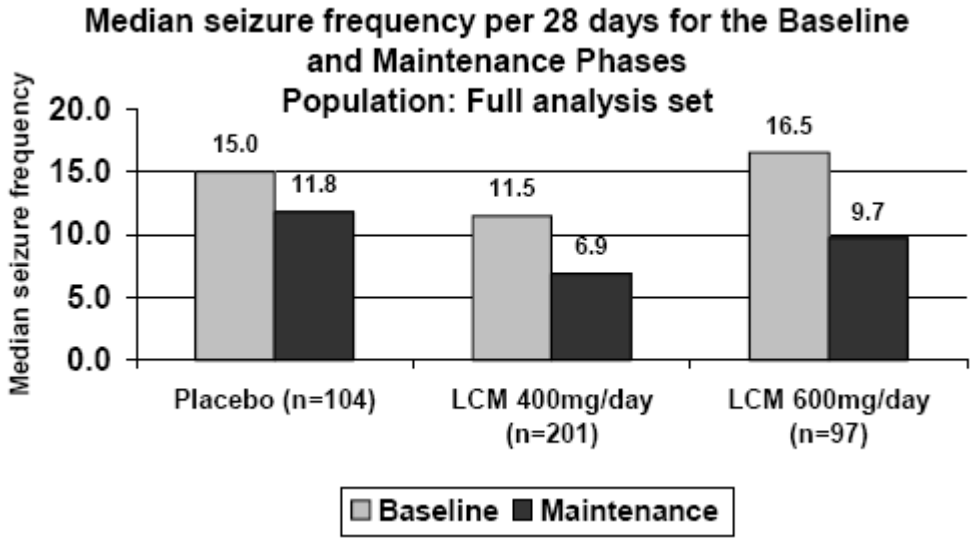
Treatment	50% responder rate (%)	Unadjusted difference compared with placebo	Odds ratio	p-value for odds ratio
Placebo	18.3	NA	NA	NA
LCM 400mg/day	38.3	20.0	2.8	0.0004**
LCM 600mg/day	41.2	23.0	3.2	0.0005**

**significant at the 0.0100 level

LCM=lacosamide; NA=not applicable

In this study, the efficacy of the two doses 400 mg/day and 600 mg/day on responder rate and seizure frequency was of similar magnitude. For the primary and some secondary efficacy variables a trend was observed towards a slightly better outcome for the 600 mg/day dose group. For one subgroup of seizures, simple partial seizures, the response to treatment in the active groups was lower than for placebo and no dose-response was observed.
The median seizure frequency per 28 days (secondary endpoint) for the baseline and maintenance phases for each treatment group is shown in figure 2.

Fig. 2. Study SP 754.The results for median seizure frequency



The results of the change in seizure frequency per 28 days at the end of the Treatment phase are presented in table 8. The treatment effect over placebo was similar for the 400 mg/day and 600 mg/day groups.

Table 8. Study SP 754. Percent reduction of seizure frequency over placebo for the maintenance phase. Full analysis set.

LCM Treatment Group	% reduction over placebo	p-value	95% CI for % reduction over placebo
400mg/day	21.6	0.0078**	(6.3, 34.5)
600mg/day	24.6	0.0061**	(7.8, 38.3)

**significant at the 0.0100 level

CI=confidence interval; LCM=lacosamide

Study SP755

A multi-centre, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of Vimpat (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization. Of the 485 randomized patients, 163 were randomized to placebo, 163 to Vimpat 200 mg/day and 159 to Vimpat 400 mg/day.
With regard to demographics, the mean age overall was 37.8 years. The majority of subjects were < 65 years old 6 subjects were ≥65 years old. Overall, 250 (51.5%) subjects were male and 235 (48.5%) subjects were female. The majority of subjects were White (99.2% of all subjects). In general, the demographic variables were balanced between groups. In the 400 mg/day group, however, the proportion of females was lower than in the other groups (400 mg/day – 43.3 %; other groups varied between 51.5 to 55.8 %).

The results for the primary efficacy parameter 50 % responder rate showed a statistically significant improvement for the 400 mg/day group. For the Vimpat 200 mg/day group, there was a strong trend but the difference was not statically significant (Table 9).

Table 9. Results for 50 % responder rates for the maintenance phase. Full analysis set population.

Treatment	50% responder rate (%)	Unadjusted difference compared with placebo	Odds ratio	p-value for odds ratio
Placebo	25.8	NA	NA	NA
LCM 200mg/day	35.0	9.2	1.6	0.0735
LCM 400mg/day	40.5	14.7	2.0	0.0063**

**significant at the 0.0100 level

LCM=lacosamide; NA=not applicable

With regard to reduction in median seizure frequency from the baseline to the maintenance phase, there was a statistically significant reduction over placebo for both the 200 mg/day and 400 mg/day doses.

For the secondary endpoint seizure-free status during the maintenance phase, the proportion of patients who were seizure free was similar in the placebo and active groups (table 10).

Table 10. Seizure-free status during the maintenance phase. Full analysis set population.

	Placebo N=159	LCM 200mg/day N=160	LCM 400mg/day N=158
	n (%)	n (%)	n (%)
Number of subjects who completed the Maintenance Phase	143 (89.9)	137 (85.6)	123 (77.8)
Number of subjects who were seizure-free during the Maintenance Phase	3 (2.1)	5 (3.6)	3 (2.4)

LCM=lacosamide

As for the other main studies, an effect was shown on the seizure subtypes complex partial and secondary generalised seizures, but not on the seizure subgroup of simple partial seizures.

- Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in subgroups

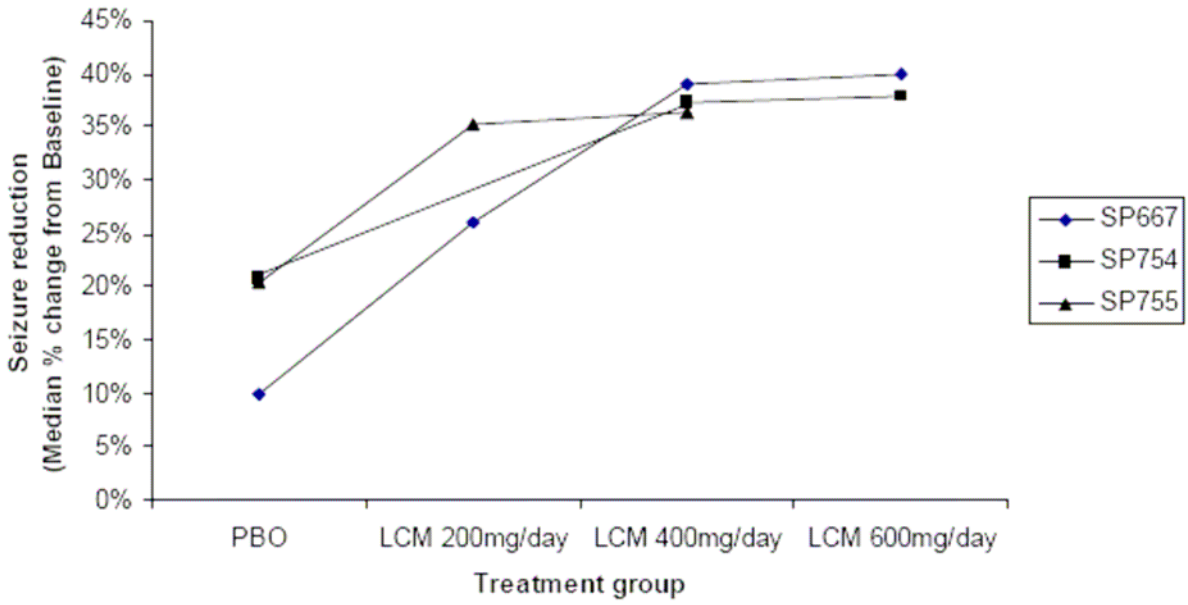
In each of the primary efficacy trials, efficacy in subgroups was evaluated. In a pooled analysis of the three main efficacy trials, the proportion of responders and the percentage reduction in seizure frequency per 28 days from baseline to the maintenance phase were similar regardless of gender, region, and number of concomitant AEDs. With regard to seizure type, however, differences were observed. Vimpat reduced the frequency of complex partial seizures and secondary generalised seizure, but had no effect on simple partial seizures.

Further to a request of the CHMP to discuss upon this issue, the applicant presented data which showed that subjects who had a reduction in complex partial seizures or partial-onset seizures with secondary generalization showed an increase in the frequency of simple partial seizures. An explanation for the lack of efficacy on simple partial seizures could thus be that complex partial or partial-onset seizures with secondary generalization change to less severe simple partial seizures in these subjects which reduces the ability to demonstrate a effect of Vimpat on simple partial seizures.

The efficacy data from the three main trials were pooled (Pool E1).

The median percent reduction in seizure frequency from baseline to maintenance phase for the three main efficacy studies is illustrated in Figure 3.

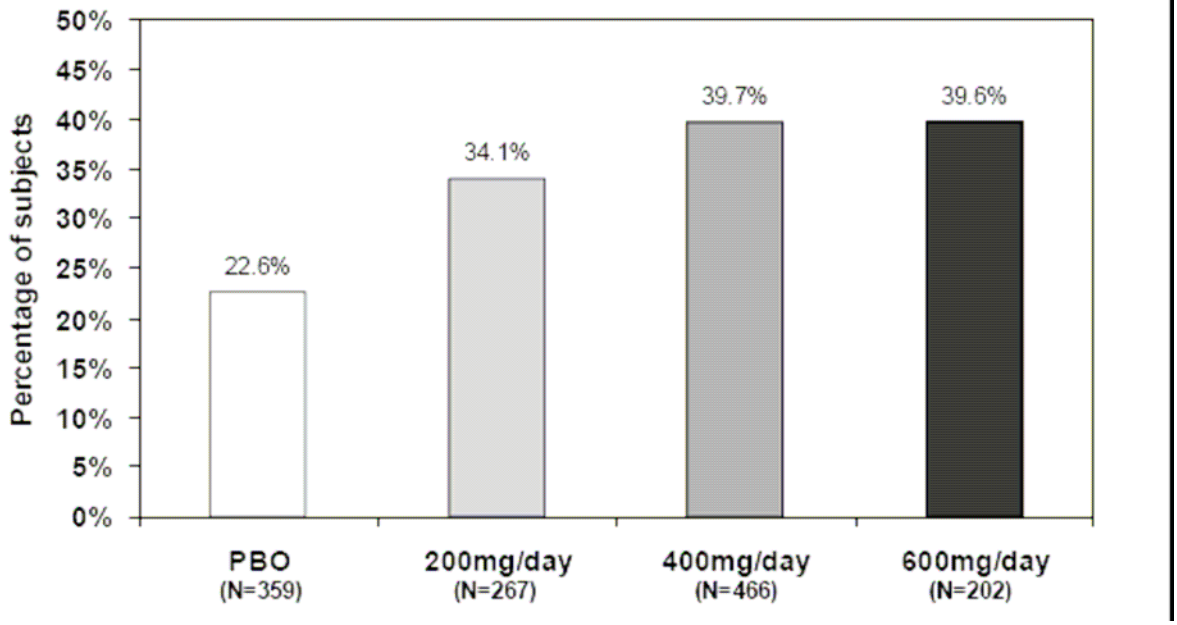
Figure 3. Median percent reduction in seizure frequency from baseline to maintenance phase by trial and treatment. Population: Full Analysis set.



FAS=Full Analysis Set; LCM=lacosamide; PBO=placebo

Figure 4 shows the pooled results for 50 % responder rate from baseline to maintenance (pool E1).

Fig. 4. Categorical response to treatment 50 % from baseline to maintenance phase in pool E1



PBO = placebo

The pooled analysis showed a statistically significant improvement for all active groups versus placebo. It is evident from Fig. 3 and 4 that there is a lack of dose-response from 400 mg/day to 600 mg/day for the primary efficacy variables.

The applicant presented results for response to treatment of ≥ 50 % and median percent reduction in seizure frequency for patients who had tried 7 or more approved AEDs. The CHMP asked the applicant to present corresponding results for patients with 1-3 and 4-6 lifetime AEDs.
The data presented showed that the median percent reduction in seizure frequency per 28 days from Baseline to Maintenance Phase was generally similar within each Vimpat treatment groups for subjects with 1 to 3, 4 to 6, or 7+ lifetime AEDs. Subjects in the placebo group who had taken 7+ lifetime AEDs had a lower median percent reduction in seizure frequency compared to subjects who had taken 1 to 3 or 4 to 6 lifetime AEDs. The response to treatment of ≥50% from Baseline to Maintenance Phase was similar among subjects with 1 to 3, 4 to 6, and 7+ lifetime AEDs within each Vimpat treatment group. Subjects who had taken 7+ lifetime AEDs had a lower placebo 50% responder rate (11.3%) than the placebo 50% responder rates observed in subjects with 1 to 3 (38.5%) or 4 to 6 (27.1%) lifetime AEDs.

Supportive studies
Study SP607 was a phase 2 multi-centre, open label, dose titration trial to determine tolerability and efficacy of SPM 927 tablets as adjunctive therapy in patients with partial seizures with or without secondary generalization. The primary objectives were to determine the maximum dose (< 600mg/day) tolerated by the majority of patients and to estimate the efficacy of oral SPM 927 when added to approved concomitant antiepileptic drugs. The trial consisted of an observational baseline Period (4 weeks), titration to maximum tolerated dose (maximum 8 weeks), and a maintenance Period (4 weeks).
In this study, 91 subjects with partial seizures with or without secondary generalization were treated with Vimpat 100-600mg/day as adjunctive on therapy for up to 91 days. The median MTD was 300 mg/day, although one quarter of the patient could tolerate doses of 600 mg/day. Interpretation of the efficacy data is difficult due to the open-label design with no data on the placebo response, and the short duration of the maintenance period (4 weeks).
There are three open-label extension trials which are all on-going. The preliminary data do not allow any safe conclusions about long-term efficacy.
The applicant will submit the final results of the long-term extension studies as a post-approval commitment.

- Discussion on clinical efficacy

A significant increase in 50 % responder rate (primary variable) as well as a statistically significant reduction of seizure frequency (secondary variable) was demonstrated in all three pivotal efficacy trials. The CHMP requested the applicant to provide supplementary efficacy analyses for 50 % responder rate in all three main trials where all patients who discontinued were regarded as failures in the responder analysis. The supplementary analyses conducted by the applicant have indicated that the efficacy data were robust.

The applicant presented the response to treatment of ≥ 50 % and median percent reduction in seizure frequency for patients who had tried 7 or more approved AEDs. Upon request of the CHMP, the applicant presented corresponding results also for patients with 1-3 and 4-6 lifetime AEDs. The results showed similar response rates for each dose of Vimpat for those subjects who had 1-3, 4-6, or > 7 lifetime AEDs.

For the 600 mg/day dose, the efficacy was very similar to the 400 mg/day dose, both for monthly seizure reduction and response to treatment 50 % from baseline. Since the safety profile for the 600 mg/day dose is worse than for the 400 mg/day dose, the risk benefit for the 600 mg/day dose was considered to be negative. Further to this consideration the applicant agreed to withdraw the 600mg/day dose from the dosing recommendations.

The efficacy data for different seizure types indicate that Vimpat is not effective for simple partial seizures. The CHMP asked the applicant to provide an explanation. The applicant's argument was that after treatment with Vimpat, complex partial or partial-onset seizures with secondary generalisation

change to less severe simple partial seizures which reduces the ability to demonstrate an effect of Vimpat on simple partial seizures. This explanation was considered adequate by the CHMP.

Three long-term extension studies are all on-going. The preliminary data do not allow any safe conclusions about development of tolerance on the long term. The applicant will submit the final study results for the long-term extension studies as a post-approval commitment.

A routine GCP inspection of Study SP755 was performed at two investigator sites (one Polish site and one Croatian site), the sponsor site and a CRO. The inspection team concluded that data documented and reported at the Polish site were credible and can be used for evaluation and assessment of the registration application whilst data obtained at the Croatian site were not reliable and cannot be used for the assessment of the authorisation application. The performance of the CRO and the sponsor in the context of clinical trial SP755 could not be considered as GCP compliant.

The applicant was asked to address how GCP issues were handled in the other two pivotal efficacy and safety studies, SP667 and SP754, and present evidence that these studies were conducted in compliance with GCP.

In response, the applicant has described general processes that were in place at the Company to ensure GCP compliance, and trial-specific processes and procedures for SP667 and SP754 that were followed to ensure GCP compliance. The applicant has also provided details on the audit program for the pivotal clinical trials SP 667 and SP 754.
An inspection performed by the FDA at the site in Croatia identified by the EMEA inspectors as not being in compliance with GCP showed similar problems with source data as have been pointed out by the EMEA inspectors. However, an FDA inspection of an additional SP755 site in Croatia did not result in any similar findings regarding source documentation.
In conclusion, the applicants response has indicated that the critical findings which were detected at the Croatian site are probably limited to that site and do not involve other sites or the other two pivotal clinical studies. This issue was therefore considered to be resolved.

On the basis of the results initially submitted by the applicant and the additional information provided during the assessment, the efficacy of Vimpat in the treatment of partial seizures is considered demonstrated.

Clinical safety

The applicant has presented safety data from the epilepsy trials in two pools of patients.

- Pool S1 (the primary safety pool) included subjects receiving at least 1 dose of trial medication (Vimpat and placebo) from the double-blind placebo controlled trials SP667, SP754, and SP755
- Pool S2 (long-term safety pool) – includes all subjects who were treated with Vimpat in the completed double-blind trials SP667, SP754, and SP755 or subjects included in the open-label trials SP607, SP615, SP756, and SP774.

The applicant presented safety data also from studies conducted in another condition, diabetic neuropathic pain (DPN).
The safety data for the pain indication are presented in a similar way. The following pooled analysis sets were used for assessing DNP safety:

- DNP Pool S1 (primary safety pool) – consists of treated DNP subjects from all double-blind placebo controlled trials.
- DNP Pool S2 (long-term safety pool) consists of all DNP subjects who were treated with Vimpat in double-blind trials SP614, SP742, SP743, and SP768 and subjects who received at least 1 dose of Vimpat in open-label trials SP665, SP745, SP746, and SP830

- Patient exposure

Patient exposure
Table 11 summarises the number of exposed subjects for the epilepsy indication and the neuropathic pain indication. A total number of 3603 subjects participated in 47 clinical trials (Phases 1 through 3) with Vimpat. A total of 1338 subjects were exposed to Vimpat in 11 Phase 2/3 trials using the oral formulation in subjects with partial-onset seizures. With regard to the Vimpat solution for infusion, a total of 199 subjects with partial-onset seizures were exposed. The 1628 subjects with neuropathic pain who were exposed to Vimpat included 1566 subjects with DNP, 25 with mixed neuropathic pain, and 37 with post-herpetic neuralgia.
The epilepsy populations and the diabetic neuropathic pain (DNP) population differ in several aspects and are not directly comparable from a safety point of view. Subjects with partial onset seizures were 20-30 years younger and generally healthier with regard to cardiovascular disease than the DNP subjects who often had underlying cardiovascular disease associated with long-standing diabetes.

Table 11. Overall exposure to Vimpat in the clinical trials

Formulation/population	**Total number of unique exposures**
Oral formulation (tablet, capsule)	
Phase 1 – oral only	608
Partial-onset seizures: Pool S2 (tablet)	1327
Partial-onset seizures: SP586/SP598 (capsule)	13[a]
DNP: DNP Pool S2	1566
Mixed neuropathic pain	25
Post-herpetic neuralgia	37
Total exposures to oral formulation (tablet, capsule)	3574
Solution for infusion	
Phase 1 iv pool	86[b]
Phase 2/3 iv pool	199[c]
Total exposures to solution for infusion	285
Total unique exposures to LCM	3603

DNP=diabetic neuropathic pain; iv=intravenous; LCM=lacosamide
a Two of these subjects rolled into SP615 in Pool S2; thus, 11 subjects in SP586/SP598 represent unique LCM exposures not counted in Pool S2.
b Of the 86 subjects in the Phase 1 iv pool, 57 subjects also received oral LCM and are counted as a Phase 1-oral exposure above; 29 received only iv LCM and were thus unique LCM exposures.
c All subjects in the Phase 2/3 iv pool were also exposed to oral LCM and are therefore also counted as an exposure to oral LCM.

The overall exposure subdivided after exposure in months is summarised in Table 12.

Table 12. Overall exposure to Vimpat stratified according to duration of exposure (months)

Population	Total subjects n (%)[a]	Subject-years of exposure[b]
Epilepsy - Pool S2		
>0 months	1327	1461.4
>6 months	898 (67.7)	1381.4
>12 months	638 (48.1)	1200.1
>24 months	248 (18.7)	719.8
>36 months	120 (9.0)	421.8
Last visit	1327 (100.0)	1371.8
DNP - DNP Pool S2		
>0 months	1566	1119.1
>6 months	895 (57.2)	992.2
>12 months	361 (23.1)	589.0
>18 months	209 (13.3)	402.9
>24 months	41 (2.6)	124.2
Post-herpetic neuralgia pool		
>0 months	37	15.8
Mixed neuropathic pain pool		
>0 months	25	28.9

DNP=diabetic neuropathic pain; LCM=lacosamide

a Percentages based on number of subjects within each respective pool exposed at least once to LCM.

b Subject-years of exposure at time points >0 months (eg, 6 months, 12 months) represents subject-years of exposure for the subjects who made it past the respective time point. For example, subject-years of exposure for >6 months includes all time on LCM, including the first 6 months of exposure, for the 898 subjects who had >6 months exposure to LCM.

Note: LCM exposure is relative to the first LCM dose and is based on all available data from visits completed as of 17 Apr 2006 (epilepsy) and 10 Feb 2006 (pain). Subject-years of exposure was defined as the total LCM exposure in days divided by 365.25. A month was defined as 28 days for the epilepsy population and 30 days for the pain population.

- Adverse events

In safety pool S1 (the 3 placebo-controlled primary trials in partial-onset seizures) treatment-emergent adverse events (TEAEs) were most common in the nervous system disorders and gastrointestinal disorders system organ classes. Dizziness, headache, and nausea were most frequent. A dose-response was observed for several common TEAEs such as dizziness, nausea, diplopia, vomiting, vision blurred, coordination abnormal, tremor, and nystagmus. The incidence of common AEs reported by > 5 % in subjects with partial onset seizures in safety pool 1 is shown in Table 13.

Table 13. Most common TEAEs for subjects with partial seizures during the treatment phase by treatment group (Pool S1)

MedDRA™ preferred term	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203	LCM Total N=944
	n (%)				
Dizziness	29 (8.0)	43 (15.9)	139 (29.5)	107 (52.7)	289 (30.6)
Headache	32 (8.8)	30 (11.1)	65 (13.8)	25 (12.3)	120 (12.7)
Nausea	16 (4.4)	20 (7.4)	53 (11.3)	35 (17.2)	108 (11.4)
Diplopia	7 (1.9)	17 (6.3)	49 (10.4)	33 (16.3)	99 (10.5)
Vomiting	9 (2.5)	16 (5.9)	40 (8.5)	32 (15.8)	88 (9.3)
Fatigue	20 (5.5)	19 (7.0)	33 (7.0)	30 (14.8)	82 (8.7)
Vision blurred	8 (2.2)	6 (2.2)	40 (8.5)	33 (16.3)	79 (8.4)
Coordination abnormal	6 (1.6)	11 (4.1)	34 (7.2)	31 (15.3)	76 (8.1)
Somnolence	17 (4.7)	14 (5.2)	38 (8.1)	16 (7.9)	68 (7.2)
Tremor	15 (4.1)	10 (3.7)	29 (6.2)	24 (11.8)	63 (6.7)
Nasopharyngitis	21 (5.8)	17 (6.3)	36 (7.6)	9 (4.4)	62 (6.6)
Nystagmus	14 (3.8)	6 (2.2)	21 (4.5)	21 (10.3)	48 (5.1)

AE=adverse event; LCM=lacosamide; MedDRA™=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Note: Treatment Phase includes both Titration and Maintenance data.
Note: Common TEAEs are defined as those AEs ocurring in ≥1% of subject in any of the LCM-treated groups within Pool S1. TEAEs presented in the table are those occurring during the Treatment Phase in ≥5% of subjects in the LCM total group.

In Pool S2 (long-term safety pool) the type of common TEAEs were comparable to those seen in Pool S1, with the most frequent TEAEs being dizziness, headache, diplopia, fatigue, and nausea. AEs were reported especially during the titration phase. The applicant should consider a revised dose titration with longer intervals between dose increases and/or smaller dose increases in order to improve tolerability.
In trials using the solution for infusion, AEs were similar to those seen with oral Vimpat. Local injection site reactions were infrequently reported.
In subjects with DNP, nervous system disorders and gastrointestinal disorders were also the most frequently affected organ systems. The most common TEAEs were dizziness, nausea, and headache. Dizziness and nausea was less frequent in the DNP trials than in the epilepsy trials, which is probably due to the fact that in the epilepsy trials Vimpat was added on to 1-3 concomitant antiepileptic drugs.

- Serious adverse event/deaths/other significant events

In the Phase 2/3 Vimpat trials in subjects with partial-onset seizures, there were a total of 4 deaths across 1338 subjects. In subjects with neuropathic pain, there were 7 deaths across 1628 subjects. All 11 deaths were considered by the investigator to be unlikely related to trial medication or not related to trial medication.
Of the 4 deaths among the partial-onset seizure population, 1 was assessed as a case of sudden unexpected death in epilepsy (SUDEP), 1 was a completed suicide, 1 was a road traffic accident, and 1 was due to intracranial hypertension. Of the 7 deaths among the DNP population, 5 were cardiac-related, 1 was a completed suicide (occurred 72 days after last dose of Vimpat), and 1 was due to pancreatic cancer.

From databases concerning 12 placebo-controlled trials for Vimpat, it emerged that 4 subjects had suicidality-related events while receiving Vimpat as compared to no events in the placebo groups. The CHMP requested the company to discuss whether a causal association with Vimpat could be excluded. From an analysis of the databases, the applicant showed that the rate of suicidality-related events in

the Vimpat clinical trial population appeared to be lower than might be expected in patients with epilepsy. The CHMP agreed that the increased risk for suicidality-related events was small and that other possible explanations could be found in these four cases. However, risk for suicidality should remain an important risk which has to be addressed via the RMP.

In Pool S1, 6.5% of Vimpat -treated subjects reported a SAE compared to 3.8% of subjects on placebo. The overall incidence of SAEs was greater in Pool S2 (15.2%) than Pool S1, which can be expected due to the longer duration of trials in Pool S2. Very few SAEs were reported in trials assessing the solution for infusion where exposure durations were short (<5 days). There was, however, one SAE of bradycardia reported in a subject who received an iv infusion during 15 minutes. In the Phase 1 trials, there was one case of a post-toxic hepatitis which occurred 12 days after the discontinuation of Vimpat. This case was considered possibly related to Vimpat.
Among subjects with DNP, the highest proportion of SAEs was in the cardiac disorders SOC, and the most commonly reported SAE was coronary artery disease in the overall population and angina unstable in the placebo-controlled trials.

Cardiac safety

PR prolongation
The results in the clinical pharmacology trials showed a dose-related increase of mean PR interval. In the thorough QT study SP640 the time of the maximum observed mean PR interval correlated to Tmax. The placebo-subtracted increase at 1 hour post-dose was 7.3 ms for the Vimpat 400 mg/day group and 11.9 ms for the Vimpat 800 mg/day group. The frequency of first degree AV block was 5.6 % in the placebo group, 3.6 % in the Vimpat 400 mg/day group but increased considerably in the Vimpat 800 mg/day group (21.2 %).

The Vimpat -induced prolongation of the PR-interval increases the risk of development of first degree AV block. Treatment-emergent first degree AV block (PR interval >209ms) was observed in 2.7% of the DNP subjects taking placebo and 8.2% of the DNP subjects taking Vimpat 400mg/day. There were two reports of truly treatment-emergent second degree AV-block in the studies for the neuropathic pain indication.

The number of different AE types and the frequency of cardiac AEs were lower in the subjects taking adjunctive Vimpat for partial-onset seizures when compared to the DNP subject group. This can be explained by differences in the study populations where partial-onset seizure subjects were 20-30 years younger and generally healthier from a cardiovascular standpoint than the diabetic neuropathic pain subjects.

Several types of treatment-emergent cardiac-related AEs were reported for the Vimpat and placebo groups in the clinical trials for DNP. In the double-blind controlled trials (DNP pool S1), treatment-emergent PR interval events, including PR prolongation (0.4%) and first degree AV block (0.5%), were only reported for the Vimpat group.

Syncope
There were 14 reports of syncope (n=8), loss of consciousness (n=4) or depressed level of consciousness (n=2) in 3 double-blind trials performed with Vimpat for the treatment of diabetic neuropathic pain (SP742, SP743, SP768). All of these patients were on Vimpat at the time of the syncopal episode, none was on placebo. Some of these subjects had increased PR intervals noted both pre- and post-syncopal episode, although no ECG was recorded during the syncopal episode. Nine of the syncopal episodes were observed in patients taking 500 mg/day or 600 mg/day.
If all Vimpat trials (double-blind and open-label) for both the epilepsy and pain indications are taken into account, a total of 43 subjects were reported to have a syncope episode while taking Vimpat. The applicant has classified these episodes of syncope in possible or probable aetiology categories. A total of 6 were classified to be of cardiac origin, 10 CNS, 2 gastro-intestinal, 2 trauma and 17 unable to categorize.

The applicant was requested to clarify if syncope in some subjects could have been due to transient episodes of AV block grade III. In response were presented analysis of ECG data from a total of 13 subjects with syncopal episodes (includes syncope, loss of consciousness and depressed level of consciousness) in all epilepsy trials that showed that in the majority of subjects, PR interval and QRS duration were within normal limits before and/or after the syncopal episode. However, in none of the subjects there was an ECG registration during the syncopal episode. In the DNP population, of the 14 subjects who had a syncopal episode, nine were taking 500 mg/day or 600 mg/day Vimpat at the time of the event. Therefore, the applicants' decision to withdraw the 600 mg/day dose from the dosing recommendations is likely to reduce the risk for syncope.

Chest pain
A total of 109 subjects were reported to have an adverse event of chest pain or chest discomfort while taking Vimpat or placebo or no drug while participating in double-blind and open-label diabetic neuropathic pain and partial seizure trials. Of these, 84 were treated with Vimpat and 25 were on placebo or no drug.
Chest pain occurred in both the relatively younger and healthier partial seizures subjects (n=51) and the older, diabetic peripheral neuropathy patients (n= 58). There was no clear correlation to dose of Vimpat. A total of 10 (12%) of the 84 subjects reported to have chest pain while taking Vimpat discontinued treatment due to the chest pain; 74 subjects continued Vimpat treatment following the report of chest pain.
The reports of chest pain did not appear to have a common aetiology. In the open-label diabetic neuropathic pain (n=3) and partial seizure (n=3) subjects, there were 6 reports of chest pain which were categorized as being of likely cardiac origin. In addition there were 2 subjects with longstanding coronary artery disease who reported chest pain. Other aetiologies for chest pain were gastrointestinal, musculoskeletal, viral and respiratory causes.
Based on the available data, the integrated analysis suggests that a cardiac origin was likely to have been the primary aetiology of chest pain in 8 (10%) of the 83 subjects with sufficient data for classification.

- Laboratory findings

The changes in laboratory findings after short-term and long-term administration of Vimpat in the partial-onset seizure population and the DNP population were similar. The observed changes in laboratory parameters are not considered to be of clinical concern.

- Safety in special populations

<u>*Age*</u>
Children and *adolescents* below 16 years with partial-onset seizures have not been studied in clinical trials and are not included in the proposed indication.

In the Phase 2/3 trials in subjects with partial-onset seizures, subjects >70 years of age were excluded.

Pharmacokinetics of Vimpat was evaluated in 23 *elderly* subjects aged 65 to 87 years in comparison with 12 young males (aged 22 to 45 years) in the SP620 trial. Following single and multiple doses (100mg twice daily for 4 days) the PK parameters AUC and Cmax in elderly males were about 30% higher than in younger males, an effect mainly caused by differences in lean body mass. The observed differences are not considered clinically relevant in the therapeutic dose range.

<u>*Gender*</u>
In the epilepsy trials, the incidence of TEAEs was higher in females than in males. AEs that were more common in females included dizziness, nausea, vomiting, coordination abnormal, nystagmus, and blurred vision. Females randomized to receive Vimpat 400mg/day or 600mg/day were also more likely than males to discontinue early for most of the common drug-associated TEAEs. In subjects with DNP, females were also more likely than males to report the common CNS and gastrointestinal effects of Vimpat, especially at higher doses of Vimpat.

Race
Non-White ethnic groups were under-represented in the database. The applicant has therefore conducted a Phase 1 trial of Vimpat to study the PK and safety in White, Black, and Asian subjects (SP 661). The results of this trial indicate that the PK of Vimpat is the same in Asian, Black, and White subjects. No clinically relevant differences were observed between the 3 ethnic groups with regard to exposure of Vimpat. The spectrum and frequencies of common side effects were similar between White and Non-White subjects.

- Safety related to drug-drug interactions and other interactions

The applicant has evaluated the change in PR interval in placebo or Vimpat -treated subjects who were also taking concomitant antiepileptic drugs which are known to increase the PR interval (lamotrigine, carbamazepine). The results of these analyses did not indicate that the PR interval increased in individuals taking lamotrigine of carbamazepine concomitantly with Vimpat compared with individuals who were not taking lamotrigine or carbamazepine.
The prolongation of the PR interval caused by administration Vimpat 400 mg/day was not changed by co-administration with digoxin.

- Discontinuation due to adverse events

In the pivotal efficacy and safety studies for the epilepsy indication (Safety Pool 1), there was a higher incidence of TEAEs leading to early discontinuation in subjects treated with Vimpat (17.1 %) than in the placebo group (4.7 %). A pronounced dose-response trend was observed with an incidence of early discontinuation of 8.1 % in the 200 mg/day group, 17.2 % in the 400 mg/day group and 28.6 % in the 600 mg/day group. Adverse events leading to discontinuation occurred most frequently in the nervous system (9.9 %) followed by GI disorders (3.2 %). The incidence of discontinuations for both nervous system disorders and GI disorders increased in a dose-dependent manner.

- Post marketing experience

There is no post marketing experience with Vimpat

- Discussion on clinical safety

The most common adverse events with Vimpat are related to the CNS and gastrointestinal system and include dizziness, nausea, vomiting, ataxia, nystagmus, coordination abnormal and tremor. Overall, there is a dose-related increase in these effects with dizziness and nausea being most frequent. Dizziness was the most common reason for discontinuation in the highest dose group. These adverse events occurred mainly during the titration phase. The applicant was asked to discuss whether a slower dose titration could be used to reduce these side effects. The applicant has presented the results of one trial where a slow titration was compared with the currently recommended dose titration. The results did not show any clear advantage for the tolerability of Vimpat by using a slower titration scheme.

The CHMP was concerned about the cardiac safety with Vimpat. Due to the dose-related increase of the PR interval with Vimpat, there is an increased risk for AV block. The increase of the PR interval was more pronounced for the DNP population which is older and has more cardiovascular disease than the epilepsy population. In the DNP Pool S1, first degree AV block was not reported in the placebo group, but occurred in 0.5 % in the two highest dose Vimpat groups. There were two reports of treatment-related second degree AV block in the neuropathic pain population at a dose of 600 mg/day and 400 mg/day, respectively. In addition, there was a dose-related increase in the occurrence of syncope with the highest incidence in the 500 and 600 mg/day groups. These syncope episodes occurred only in subjects treated with Vimpat in DNP placebo-controlled trials but not in the placebo groups. The applicant was asked to clarify if syncope in some subjects could have been due to transient episodes of AV block grade III. The analysis provided by the applicant has not indicated that AV block III was a cause of syncope. The CHMP asked if it was possible in the clinical situation to identify patients that are at high risk of developing PR prolongation and AV block with Vimpat. The

applicant's analyses showed that it is not possible to identify this group of patients before treatment with Vimpat is initiated.

Treatment with Vimpat was associated with chest pain, although no clear correlation do dose was reported. Further to a CHMP request, the applicant has reanalysed the frequency and causes of chest pain in the epilepsy population. The chest pain was often of long duration, and no ECG evidence of ischemia or infarction was reported among those patients who had treatment-emergent chest pain in the placebo-controlled studies. Chest pain was not more common in the DNP trials than in the epilepsy trials. Although the mechanism behind chest pain remains obscure, cardiac aetiology appears to be rare.

For one of the 5 deaths in the DNP population that were related to cardiovascular causes, supplementary information was provided in by the applicant during the assessment procedure. The response showed that the patient had multiple risk factors for cardiovascular disease. There was no important prolongation of the PR interval in consecutive ECG recordings taken before the subject's death.

The possible association between use of AEDs and suicidality-related events is questioned (see recent FDA review on antiepileptic drugs and suicidality, 23 May 2008). The CHMP asked the applicant to argue upon the potential concern related to suicidality events with the use of Vimpat. The applicant showed that the rate of suicidality-related events in the Vimpat clinical trial population appeared to be lower than might be expected in patients with epilepsy. The CHMP agreed that the increased risk for suicidality-related events was small and that other possible explanations could be found for the four cases reported. However, risk for suicidality should remain an important risk which has to be addressed via the RMP. Furthermore, the applicant committed to submit variation to include agreed class labelling wording in the EU in SPC/Package Leaflet of Vimpat, following finalisation of the class review of antiepileptic medicinal products regarding suicidality by the CHMP.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reactions suspected of occurring either in the European Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The applicant plans to use routine pharmacovigilance with the exception of the cardiovascular adverse events related to PR prolongations, for which enhanced pharmacovigilance measures will be applied. Cardiovascular and psychiatric events, including AV block, syncope, bradycardia, PR prolongation, depression, abuse liability and suicide/suicide attempts will require a medical follow-up to ensure that appropriate data are collected and to characterize and assess the cases. To this end, the applicant will conduct of a post approval safety study (SP942).

Two of the potential concerns ("potential for hepatotoxicity" and "potential for worsening of seizures") may be considered AED class effects, and have not been demonstrated as identified risks in the LCM development program. These observations have been classified as potential concerns because of the uncertainty in extrapolating risk from a clinical development program to the population at large. Hence, routine pharmacovigilance is considered an appropriate measure to monitor for any unexpected long-term safety signals for these potential concerns.

The remaining potential safety concerns ("limited use in pregnant or lactating women" and "no use in children and adolescents") are included per guidance due to limited exposure. Both groups will be

specifically excluded from recommended use in the proposed product labelling. Hence, routine pharmacovigilance is considered adequate to appropriately monitor long-term safety for these potential concerns.

The CHMP requested the applicant to add two potential safety concerns to the RMP, the potential increased risk for suicidality-related events and the potential abuse liability. The first, and most important, is considered to be a class-related effect and, although the enhanced risk may be small, it can not be ignored. The abuse liability might be not a major problem, but as Vimpat is a centrally-acting drug with novel mechanism of actions, it deserves to be addressed in the RMP.
The applicant will also update a post-authorisation safety study (SP942) to include both the above identified potential safety concerns.

Safety Specification
A total of eight safety concerns have been identified by the applicant. They include cardiac adverse events, potential hepatotoxicity, potential for worsening of seizures, dizziness, potential for abuse as a CNS-active product, potential for suicidality as an anti-epileptic product, limited use in pregnant and lactating women and no use in adolescents and children.

Enhanced pharmacovigilance actions will be employed what concerns cardiac adverse events focusing on PR interval prolongation. Cardiac events (e.g. second or third degree heart block and syncope) which will be monitored as medical events of interest, and medical follow-up will ensure appropriate data are collected to characterize and assess the case. The applicant will implement the standardized MedDRA Queries for the preferred terms of atrioventricular block, PR interval prolongation, bradycardia and syncope. These events will be reviewed on a case-by-case basis. The applicant will provide systematic reviews on PR prolongation and potentially associated symptoms with in the PSUR system

Risk minimisation plan
Routine risk minimization activities are proposed for areas of limited experience and for potential safety concerns that need to be better characterized. No other risk minimization activities are planned.

The Risk Management Plan and Minimization Plan with proposed activities are summarised below.

Table Summary of the risk management plan

Summary of the Risk Management Plan and Risk Minimization Plan for LCM			
Safety Concern	**Proposed Pharmacovigi-lance Activities**	**Mile-stones**	**Proposed Risk Minimization Activities**
Cardiac adverse events which may be potentially associated with PR interval prolongation and sodium channel modulation	Enhanced and routine pharmacovigilance Non-interventional post-authorization safety study	PSURs	**SPC Section 4.3** Contraindication for known second- or third-degree atrioventricular (AV) block. **SPC Section 4.4** Information on prolongations in PR interval 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. **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 (e.g. atrioventricular block, syncope, bradycardia) may occur. **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.
Potential hepatotoxicity	Routine pharmacovigilance	PSURs	**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	PSURs	NA
Dizziness	Routine pharmacovigilance	PSURs	**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.

Potential for abuse as a CNS-active product	Routine pharmacovigilance Non-interventional post-authorization safety study	PSURs	NA
Potential for suicidality as an anti-epileptic product	Routine pharmacovigilance Non-interventional post-authorization safety study	PSURs	NA
Limited use in pregnant or lactating women	Routine pharmacovigilance Pregnancy registry	PSURs	**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.
No use in children and adolescents	Routine pharmacovigilance	NA	**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.

NA=not applicable; PSUR=Periodic Safety Update Report; SPC=Summary of Product Characteristics

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

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
As requested by the CHMP, the applicant committed to initiate a development program to remove the preservative propyl parahydroxy benzoate sodium from the formulation of the lacosamide syrup and to submit the necessary regulatory application as a post-approval Follow-Up measure in order to register the reformulated syrup in the agreed time frame. There are a number of unresolved minor quality issues but these do not have a negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

The mechanism of action of Vimpat is considered unknown. Two mechanisms of actions have been suggested by the applicant which so far are considered as hypothesis: 1) Binding to the collapsin response mediator protein-2 which is involved in neuronal differentiation and control of axonal outgrowth. 2) Enhancement of sodium channel slow inactivation without effects on fast inactivation which might facilitate control of neuronal hyperexcitability.

In vivo, Vimpat has demonstrated support for the proposed indication in relevant models of seizure disorders for generalised tonic-clonic disorders and complex partial seizures. A less marked effect was noted in a model for status epilepticus, while Vimpat is without effect in absence seizures.

Safety pharmacology studies in the CNS showed a dose-dependent behavioural depressant effect, accompanied by a decrease in muscle tone. Cardiovascular *in vivo* studies demonstrated a cardiodepressant action including decreases in blood pressure, contractility and cardiac output,

slowing of atrial and ventricular conductivity, and, at very high doses, atrioventricular block and atrioventricular dissociation.

Lacosamide was rapidly absorbed and widely distributed in mice, rats and dogs. Lacosamide distributed mainly to the organs of metabolism and excretion, kidneys, liver and gall bladder. In general, pharmacokinetic parameters did not differ between genders or single or repeat dose administration. No repeat-dose distribution studies were included. However, valid justification was provided by the applicant. Furthermore, no obvious signs of accumulation were evident in any tissue. The protein binding was low (<15%) in all tested species. Lacosamide is metabolised by CYP2C19, but to a low extent. In humans, the major part of the dose was excreted as unchanged lacosamide and SPM 12809, and smaller amounts consisted of SPM 6912 and its N-carbamoyl glucuronide, O-desmethyl hydroxyl and p-hydroxy metabolites. The animal species tested formed the metabolites in humans; hence mice, rats and dogs are suitable species for the toxicity studies.

Lacosamide has been tested in a full set of toxicity studies, where the pivotal studies have been performed according to GLP standards. In principle, in most studies and in all species tested, the central nervous system effects of lacosamide have been dose limiting, hence other signs of toxicity were scarce. Also, as a consequence of the low dose levels, the margins over human clinical maximum exposure in respect to Cmax and AUC are low or non-existent.
In mice, no specific target organ was identified. In rats, the liver was the target organ, showing adaptive enzyme induction effects. In the dogs, the target organ was the heart, with increase heart rate, decreased arterial systolic blood pressure and one case of a second degree AV heart block in the 2-week intravenous study. Heart toxicity has also been seen in the clinic.

Lacosamide was tested for genotoxicity and/or mutagenicity using three *in vitro* and two *in vivo* tests. The weight of evidence is sufficient to conclude that lacosamide poses no genotoxic potential.

Lacosamide did not hold a carcinogenic potential when tested in 2-year studies in rats and mice.

In rats and rabbits, no teratogenic effects were seen under the present study conditions. However, the value of these studies in regard to evaluate the possible teratogenicity in rats and rabbits and the potential risk for humans, is severely hampered by the fact that central nervous system effects in the dams were dose limiting. The doses possible to administer, and the exposures reached left small or non-existent margins over human exposure. At maternal toxic doses, embryo-toxicity was seen. In addition, on basis of the submitted studies in juvenile rats, a potential for reproductive and neurological developmental toxicity can not be ruled out.

Based on results from abuse liability studies, it was the opinion of the CHMP that lacosamide is unlikely to hold a potential for behavioural and/or physical dependence on withdrawal.

As for the environmental risk assessment, since lacosamide is not readily biodegradable, the applicant will submit the results of an ongoing aerobic water sediment study (OECD 308) as a post approval follow-up measure.

Efficacy

The applicant has performed three placebo-controlled trials with parallel group design to investigate the efficacy of lacosamide as adjunctive treatment for partial-onset seizures. In general, the design of these studies was in accordance with the EMEA guideline for medicinal products in the treatment of epileptic disorders (CPMP/EWP566/98 rev 1, 2000). The dose-response trial SP667 showed a dose-response from 200 mg/day to 400 mg/day but no dose-response relationship between the 400 mg/day and 600 mg/day doses for the primary efficacy variable.
With regard to the primary efficacy variable, pooled results from the three main studies showed that 34% of patients treated with Vimpat 200 mg/day and 40% of patients treated with Vimpat 400 mg/day showed response to treatment *vs* 23% in the placebo group. Considering the two individual studies where the lowest dose 200 mg/day was investigated, there was no difference from placebo with regard to the primary efficacy variable but in a pooled analysis statistical significance was achieved. A

statistically significant reduction of seizure frequency (secondary efficacy variable) was also demonstrated in all three pivotal efficacy trials.
In response to a CHMP request the applicant has provided supplementary efficacy analyses for 50 % responder rate in all three main trials where all patients who discontinued are regarded as failures in the responder analysis. The supplementary analyses have indicated that the efficacy data were robust.
The applicant has also presented the response to treatment of ≥ 50 % and median percent reduction in seizure frequency for patients who had tried 7 or more approved AEDs. Upon request of the CHMP, the applicant presented corresponding results also for patients with 1-3 and 4-6 lifetime AEDs. The results showed similar response rates for each dose of lacosamide for those subjects who had 1-3, 4-6, or > 7 lifetime AEDs.
For the 600 mg/day dose, the efficacy was very similar to the 400 mg/day dose, both for monthly seizure reduction and response to treatment 50 % from baseline. Since the safety profile for the 600 mg/day dose is worse than for the 400 mg/day dose, the risk benefit for the 600 mg/day dose was considered to be negative. Further to this consideration the applicant has decided to withdraw the 600mg/day dose from the dosing recommendations.
The efficacy data for different seizure types indicate that lacosamide is not effective for simple partial seizures. The CHMP accepted the argument of the applicant, that after treatment with lacosamide, complex partial or partial-onset seizures with secondary generalisation change to less severe simple partial seizures which reduces the ability to demonstrate an effect of Vimpat on simple partial seizures.
Three long-term extension studies are all on-going. The preliminary data do not sufficient to conclude on the development of tolerance on the long term. The applicant will submit the final study results for the long-term extension studies as a post-approval commitment.

Further to a routine GCP inspection, the clinical results from one site of Study SP 755 (pivotal) where considered not reliable and therefore excluded from the assessment. The exclusion of data from this site does not affect the overall results. The applicant gave adequate reassurance to the CHMP that the critical findings did not concern other sites or the other two pivotal studies.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The most common adverse events with lacosamide are related to the CNS and gastrointestinal system and include dizziness, nausea, vomiting, ataxia, nystagmus, coordination abnormal and tremor. Overall, there is a dose-related increase in these effects with dizziness and nausea being most frequent. Dizziness was the most common reason for discontinuation in the highest dose group. These adverse events occurred mainly during the titration phase. The applicant was asked to discuss whether a slower dose titration could be used to reduce these side effects. The applicant has presented the results of one trial where a slow titration was compared with the currently recommended dose titration. The results did not show any clear advantage for the tolerability of Vimpat by using a slower titration scheme. The CHMP was concerned with regard to the cardiac safety with lacosamide. Due to the dose-related increase of the PR interval with lacosamide, there is an increased risk for AV block. The increase of the PR interval was more pronounced for the DNP population which is older and has more cardiovascular disease than the epilepsy population. In the DNP Pool S1, first degree AV block was not reported in the placebo group, but occurred in 0.5 % in the two highest dose lacosamide groups. There were two reports of treatment-related second degree AV block in the neuropathic pain population at a dose of 600 mg/day and 400 mg/day, respectively.
In addition, there was a dose-related increase in the occurrence of syncope with the highest incidence in the 500 and 600 mg/day groups. These syncope episodes occurred only in subjects treated with lacosamide in DNP placebo-controlled trials but not in the placebo groups. The applicant was asked to clarify if syncope in some subjects could have been due to transient episodes of AV block grade III. The analysis provided by the applicant has not indicated that AV block III was a cause of syncope. The CHMP asked if it was possible in the clinical situation to identify patients that are at high risk of developing PR prolongation and AV block with Vimpat. The applicant's analyses showed that it is not possible to identify this group of patients before treatment with Vimpat is initiated.

Treatment with Vimpat was associated with chest pain, although no clear correlation to dose was reported. Further to a CHMP request, the applicant has reanalysed the frequency and causes of chest pain in the epilepsy population. The chest pain was often of long duration, and no ECG evidence of ischemia or infarction was reported among those patients who had treatment-emergent chest pain in the placebo-controlled studies. Chest pain was not more common in the DNP trials than in the epilepsy trials. Although the mechanism behind chest pain remains obscure, cardiac aetiology appears to be rare.
For one of the 5 deaths in the DNP population that were related to cardiovascular causes, supplementary information was provided in by the applicant during the assessment procedure. The response showed that the patient had multiple risk actors for cardiovascular disease. There was no important prolongation of the PR interval in consecutive ECG recordings taken before the subject's death.
For the intravenous formulation of Vimpat, the spectrum of adverse events was similar to the oral formulation. Local tolerability appears to be acceptable.
Review of suicidality-related events showed that the risk of those events was lower than might be expected in patients with epilepsy, and that other possible explanations could be found. However, risk for suicidality should remain an important risk which has to be addressed via the RMP. Moreover, the applicant committed to include agreed class labelling wording in the EU in SPC/Package Leaflet of Vimpat, following finalisation of the class review of antiepileptic medicinal products regarding suicidality by the CHMP.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user test consultation provided is satisfactory.

Risk-benefit assessment

Lacosamide enhances slow inactivation of sodium channel without effects on fast inactivation, a mechanism which has not been described earlier. However, in animal models predicting seizure disorder an effect identical to phenytoin and almost identical to lamotrigine was demonstrated. At present, the clinical relevance of the observed slow inactivation of the sodium channel versus fast inactivation (e.g. phenytoin) can not be determined.

Lacosamide appears to have favourable pharmacokinetics with fast oral absorption, full bioavailability, low protein binding, dose- and time-independent kinetics and elimination through both metabolism and renal excretion. No circulating pharmacologically active metabolites have been identified. The interaction potential appears low but an *in vivo* study with a CYP3A4 substrate is planned to study the possibility of weak to moderate induction and inhibition of this enzyme. The elimination of lacosamide has not been fully characterised. There are few identified situations with increased lacosamide exposure.

In non-clinical toxicity studies a dose-related CNS depressant effect was dose-limiting resulting in exposure margins at or below clinical exposure. In mice, no specific target organ was identified. In rats, the liver was the target organ. In dogs, the target organ was the heart, with increase heart rate, decreased arterial systolic blood pressure and one case of a second degree AV heart block in the 2-week intravenous study. Further preclinical studies regarding heart safety would not add any relevant information to the overall risk/benefit of the patient.

The systemic exposure of metabolites has been only roughly characterised and elimination pathways of Vimpat have not been completely characterised. There were some indications of CYP3A4 inhibition and induction *in vitro* and the applicant plans to perform an interaction study with oral midazolam to investigate the *in vivo* relevance of these findings.

In a small, single-dose, renal impairment study, the exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure could give rise to adverse effects but no pharmacological activity of the metabolite has been observed.

In three pivotal efficacy studies with parallel group design, 34% of patients treated with Vimpat 200 mg/day and 40% of patients treated with Vimpat 400 mg/day showed response to treatment *vs* 23% in the placebo group. For the 200 mg/day dose, the differences versus placebo for the primary endpoint were not statistically significant in the two individual studies but achieved significance in a pooled analysis. For the 400 mg/day dose, a statistically significant difference versus placebo was demonstrated in all three trials. The 600 mg/day dose has been withdrawn from the dosing recommendations due to an unfavourable benefit/risk ratio. The antiepileptic effect of Vimpat as adjunctive treatment of partial seizures has been satisfactorily documented. Although there are no comparative studies, the effect of Vimpat on 50 % responder rate appears to be of similar magnitude as for some other approved antiepileptic drugs. The GCP issues which concern the CRO and sponsor in the context of the inspected clinical trial SP755 was considered resolved.

In the three placebo-controlled primary efficacy trials in partial-onset seizures, treatment-emergent adverse events were most common in the nervous system and gastrointestinal system organ classes. Dizziness, headache, and nausea were most frequent. A dose-response was observed for several common adverse events. Adverse events like dizziness and nausea occurred especially during the titration phase.
Vimpat causes a dose-related increase in the PR interval with increased risk for atrio-ventricular blockade. An increased incidence of atrio-ventricular block I and II was observed in lacosamide-exposed subjects in the diabetic neuropathic pain trials.
There was also an increased incidence of syncopal episodes in lacosamide-exposed subjects, especially at high lacosamide doses and in the diabetic neuropathic pain population where patients are older and have more cardiovascular disease than in the epilepsy population.
Known atrio-ventricular block II and III should be included as contraindications to treatment with lacosamide.
Treatment with Vimpat was associated with chest pain, although no clear correlation to dose was reported. The underlying mechanism for lacosamide-induced chest pain is not clear, but cardiac aetiology appears to be rare.
At present the risk of suicidality-related event is not of concern; however, it will be included in the RMP and the applicant will address this issue also in a post-approval study. Furthermore, the applicant will submit variation to include agreed class labelling wording in the EU in SPC/Package Leaflet of Vimpat, following finalisation of the class review of antiepileptic medicinal products regarding suicidality by the CHMP.
Three long-term extension studies are all on-going. The preliminary data do not allow any reliable conclusions about development of tolerance on the long term or long-term safety. The applicant should submit the final study results for the long-term extension studies as a post-approval commitment.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Vimpat *as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older* was favourable and therefore recommended the granting of the marketing authorisation.