ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Pinkish, oval film-coated tablets debossed with ‘SP’ on one side and ‘50’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).
Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic

effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution.
In patients with severe renal impairment ($CL_{CR} \leq 30$ ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide film-coated tablets are for oral use. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics . However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosamide does not inhibit or induce CYP2C19 and 3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily), but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g.

fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo*, but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility

No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[(1)]
Immune system disorders			Drug hypersensitivity[(1)]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [(1,2)]
Psychiatric disorders		Depression Confusional state Insomnia[(1)]	Aggression[(1)] Agitation[(1)] Euphoric mood[(1)] Psychotic disorder[(1)] Suicide attempt [(1)] Suicidal ideation [(1)] Hallucination [(1)]	

Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope [(2)]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[(1,2)] Bradycardia[(1,2)] Atrial Fibrillation [(1,2)] Atrial Flutter [(1,2)]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [(2)] Hepatic enzyme increased (> 2x ULN) [(1)]	
Skin and subcutaneous tissue disorders		Pruritus Rash[(1)]	Angioedema[(1)] Urticaria[(1)]	Stevens-Johnson syndrome[(1)] Toxic epidermal necrolysis[(1)]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[(1)] Adverse reactions reported in post marketing experience.
[(2)] See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is

uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression, but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.

- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy
Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.
The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing

antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor. The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the

feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected..
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of

hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat
polyvinyl alcohol
polyethylene glycol 3350
talc
titanium dioxide (E171)
red iron oxide (E172)
black iron oxide (E172)
indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of 14, 28, 56 and 168 film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Packs of 14 x 1 and 56 x 1 film-coated tablet in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/001-003
EU/1/08/470/020
EU/1/08/470/024
EU/1/08/470/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Dark yellow, oval film-coated tablets debossed with ‘SP’ on one side and ‘100’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).
Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the

potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in older patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment ($CL_{CR} \leq$30 ml/min) and in patients with endstage renal disease,a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide film-coated tablets are for oral use. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also

shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics. However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daiy).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead

to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility

No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[(1)]
Immune system disorders			Drug hypersensitivity[(1)]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [(1,2)]
Psychiatric disorders		Depression Confusional state Insomnia[(1)]	Aggression[(1)] Agitation[(1)] Euphoric mood[(1)] Psychotic disorder[(1)] Suicide attempt [(1)] Suicidal ideation [(1)] Hallucination [(1)]	

Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope [(2)]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[(1,2)] Bradycardia[(1,2)] Atrial Fibrillation [(1,2)] Atrial Flutter [(1,2)]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [(2 Hepatic enzyme increased (> 2x ULN) [(1))]	
Skin and subcutaneous tissue disorders		Pruritus Rash[(1)]	Angioedema[(1)] Urticaria[(1)]	Stevens-Johnson syndrome[(1)] Toxic epidermal necrolysis[(1)]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[(1)] Adverse reactions reported in post marketing experience.
[(2)] See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is

uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptom, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.

- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy
Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 %

and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor.
The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours. The

pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and

triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat
polyvinyl alcohol
polyethylene glycol 3350
talc
titanium dioxide (E171)
yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of 14, 28, 56 and 168 film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Packs of 14 x 1 and 56 x 1 film-coated tablet in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/004-006
EU/1/08/470/021
EU/1/08/470/026
EU/1/08/470/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Salmon, oval film-coated tablets debossed with 'SP' on one side and '150' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening). Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic

effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment (CL_{CR} ≤30 ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day is recommended.. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment.A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide film-coated tablets are for oral use. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics . However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g.

fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility

No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[(1)]
Immune system disorders			Drug hypersensitivity[(1)]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [(1,2)]
Psychiatric disorders		Depression Confusional state Insomnia[(1)]	Aggression[(1)] Agitation[(1)] Euphoric mood[(1)] Psychotic disorder[(1)] Suicide attempt [(1)] Suicidal ideation [(1)] Hallucination [(1)]	

Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope [(2)]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[(1,2)] Bradycardia[(1,2] Atrial Fibrillation [(1,2)] Atrial Flutter [(1,2)]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [(2)] Hepatic enzyme increased (> 2x ULN) [(1)]	
Skin and subcutaneous tissue disorders		Pruritus Rash[(1)]	Angioedema[(1)] Urticaria[(1)]	Stevens-Johnson syndrome[(1)] Toxic epidermal necrolysis[(1)]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[(1)] Adverse reactions reported in post marketing experience.
[(2)] See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is

uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in.these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944)treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.

- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy
Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.
The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing

antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*.. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor.
The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the

feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.
A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and

triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat
polyvinyl alcohol
polyethylene glycol 3350
talc
titanium dioxide (E171)
yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of 14, 28 and 56 film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Multipacks containing 168 (3 packs of 56 tablets) film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Packs of 14 x 1 and 56 x 1 film-coated tablet in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/007-009
EU/1/08/470/022
EU/1/08/470/028
EU/1/08/470/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Blue, oval film-coated tablets debossed with ‘SP’ on one side and ‘200’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).
Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the

potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment (CL_{CR} ≤30 ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide film-coated tablets are for oral use. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also

shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics . However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily.) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but

are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility

No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[(1)]
Immune system disorders			Drug hypersensitivity[(1)]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [(1,2)]
Psychiatric disorders		Depression Confusional state Insomnia[(1)]	Aggression[(1)] Agitation[(1)] Euphoric mood[(1)] Psychotic disorder[(1)] Suicide attempt [(1)] Suicidal ideation [(1)] Hallucination [(1)]	

Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus HypoesthesiaDysarthria Disturbance in attention Paraesthesia	Syncope [(2)]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[(1,2)] Bradycardia[(1,2)] Atrial Fibrillation [(1,2)] Atrial Flutter [(1,2)]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [(2)] Hepatic enzyme increased (> 2x ULN) [(1)]	
Skin and subcutaneous tissue disorders		Pruritus Rash[(1)]	Angioedema[(1)] Urticaria[(1)]	Stevens-Johnson syndrome[(1)] Toxic epidermal necrolysis[(1)]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[(1)] Adverse reactions reported in post marketing experience.
[(2)] See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is

uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.

- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy
Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.
The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing

antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*.. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor.
The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the

feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of

hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat
polyvinyl alcohol
polyethylene glycol 3350
talc
titanium dioxide (E171)
indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of 14, 28 and 56 film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Multipacks containing 168 (3 packs of 56 tablets) film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.
Packs of 14 x 1 and 56 x 1 film-coated tablet in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/010-012
EU/1/08/470/023
EU/1/08/470/030
EU/1/08/470/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Treatment initiation pack
Vimpat 50 mg film-coated tablets
Vimpat 100 mg film-coated tablets
Vimpat 150 mg film-coated tablets
Vimpat 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg lacosamide.
Each film-coated tablet contains 100 mg lacosamide.
Each film-coated tablet contains 150 mg lacosamide.
Each film-coated tablet contains 200 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
50 mg:
Pinkish, oval film-coated tablets debossed with ‘SP’ on one side and ‘50’ on the other side.
100 mg:
Dark yellow, oval film-coated tablets debossed with ‘SP’ on one side and ‘100’ on the other side.
150 mg:
Salmon, oval film-coated tablets debossed with ‘SP’ on one side and ‘150’ on the other side.
200 mg:
Blue, oval film-coated tablets debossed with ‘SP’ on one side and ‘200’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).
Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Vimpat treatment initiation pack contains 4 different packages (one for each tablet strength) with 14 tablets each, for the first 2 to 4 weeks of therapy depending on the patient´s response and tolerability. The packages are marked with 'week 1 (2, 3 or 4)'.
On the first day of treatment the patient starts with Vimpat 50 mg tablets twice a day. During the second week, the patient takes Vimpat 100 mg tablets twice a day.
Depending on response and tolerability, Vimpat 150 mg tablets may be taken twice a day during the third week and Vimpat 200 mg tablets twice a day during the fourth week.

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). A maximum dose of 250 mg/day is recommended for patients with severe renal impairment ($CL_{CR} \leq$30 ml/min) and in patients with endstage renal disease. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity). In all patients with renal impairment, the dose titration should be performed with caution (see section 5.2).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide film-coated tablets are for oral use. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics. However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily.) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the

pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility
No adverse reactionts on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[(1)]
Immune system disorders			Drug hypersensitivity[(1)]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [(1,2)]
Psychiatric disorders		Depression Confusional state	Aggression[(1)] Agitation[(1)]	

		Insomnia[1]	Euphoric mood[1] Psychotic disorder[1] Suicide attempt [1] Suicidal ideation [1] Hallucination [1]	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus HypoesthesiaDysarthria Disturbance in attention Paraesthesia	Syncope [2]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[1,2] Bradycardia[1,2] Atrial Fibrillation [1,2] Atrial Flutter [1,2]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [2] Hepatic enzyme increased (> 2x ULN) [1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema[1] Urticaria[1]	Stevens-Johnson syndrome[1] Toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[1] adverse reactions reported in post marketing experience.
[2] See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.
- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management

There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action

The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated.

In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects

Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.

In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety

Monotherapy

Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.

The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.

The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*.. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor. The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and

biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and

triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat
polyvinyl alcohol
polyethylene glycol 3350
talc
titanium dioxide (E171)

50 mg tablets: red iron oxide (E172), black iron oxide (E172), indigo carmine aluminium lake (E132)
100 mg tablets: yellow iron oxide (E172)
150 mg tablets: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)
200 mg tablets: indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC blister sealed with an aluminium foil.
The treatment initiation pack contains 4 cartons, each carton with 14 tablets of 50 mg, 100 mg, 150 mg and 200 mg

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 10 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of syrup contains 10 mg lacosamide.
1 bottle of 200 ml contains 2,000 mg lacosamide.
1 bottle of 465 ml contains 4,650 mg lacosamide.

Excipients with known effect:
Each ml of Vimpat syrup contains 187 mg sorbitol (E420), 2.60 mg sodium methyl parahydroxybenzoate (E219), 0.032 mg aspartame (E951), and 1.42 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.
A slightly viscous clear, colourless to yellow-brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).
Lacosamide may be taken with or without food.

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose

Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment (CL_{CR} ≤30 ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. . The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Lacosamide syrup must be taken orally.

The bottle containing Vimpat syrup should be shaken well before use.
Only the measuring cup provided in this pack should be used for dosing of Vimpat syrup 10 mg/ml. Each graduation mark (5ml) of the measuring cup corresponds to 50 mg lacosamide. Lacosamide may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

Vimpat syrup contains sodium methyl parahydroxybenzoate (E219), which may cause allergic reactions (possibly delayed).). It contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine. The syrup contains aspartame (E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. It contains sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics. However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6,

and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent.
Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility
No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[1]
Immune system disorders			Drug hypersensitivity[1]	Drug reaction with eosinophilia and systemic symptoms (DRESS)[1,2]
Psychiatric disorders		Depression Confusional state Insomnia[1]	Aggression[1] Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt[1] Suicidal ideation[1] Hallucination[1]	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[1,2] Bradycardia[1,2] Atrial Fibrillation[1,2] Atrial Flutter[1,2]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal[2] Hepatic enzyme increased (> 2x ULN)[1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema[1] Urticaria[1]	Stevens-Johnson syndrome[1] Toxic epidermal necrolysis[1]
Musculoskeletal and connective		Muscle spasms		

tissue disorders				
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

(1) adverse reactions reported in post marketing experience.
(2) See Description of selected adverse reactions.

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in. these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.
- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy
Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.
The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted

absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C_{max} about 0.5 to 4 hours post-dose. Vimpat tablets and syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of

additional metabolites were found in the urine.
In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*.. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor.
The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.
A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Carmellose sodium
Sorbitol liquid (crystallizing) (E420)
Polyethylene glycol 4000
Sodium chloride
Citiric acid, anhydrous
Acesulfame potassium (E950)
Sodium methyl parahydroxybenzoate (E219)
Strawberry flavour (contains propylene glycol, maltol)
Masking flavour (contains propylene glycol, aspartame (E951), acesulfame potassium (E950), maltol deionised water)
purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
After first opening: 4 weeks.

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

200 ml and 465 ml amber glass bottles with white polypropylene screw cap and a measuring cup. Each graduation mark (5ml) of the measuring cup corresponds to 50 mg (for example 2 graduation marks correspond to 100 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/018-019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 10 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 10 mg lacosamide.
Each vial of 20 ml solution for infusion contains 200 mg lacosamide.

Excipients with known effect:
Each ml of solution for infusion contains includes 2.99 mg sodium.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Lacosamide therapy can be initiated with either oral or i.v. administration. Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with i.v. lacosamide is at the physician's discretion; there is experience from clinical trials with twice daily infusions of lacosamide for up to 5 days in adjunctive therapy. Monitor closely patients with known cardiac conduction problems, on concomitant medications that prolong PR interval, or with severe cardiac disease (e.g. myocardial ischemia, heart failure) when lacosamide dose is higher than 400 mg/day (see Method of administration below and section 4.4).
Lacosamide must be taken twice a day (usually once in the morning and once in the evening).

Monotherapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.
Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy
The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation
In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Conversion to or from oral and intravenous administration can be done directly without titration. The total daily dose and twice daily administration should be maintained.

Special populations

Elderly (over 65 years of age)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8, and 5.1).

Renal impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment (CL_{CR} ≤30 ml/min) and in patients with endstage renal disease, a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment
A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population
The safety and efficacy of lacosamide in children aged below 16 years have not yet been established. No data are available.

Method of administration
Product with particulate matter or discolouration should not be used.
The solution for infusion is infused over a period of 15 to 60 minutes twice daily. An infusion duration of at least 30 minutes for administration >200 mg per infusion (i.e. >400 mg/day) is preferred.
Vimpat solution for infusion can be administered intravenously without further dilution or can be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) solution for injection or lactated Ringer's solution for injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction
Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however both have been reported in open-label epilepsy trials and in post-marketing experience (see section 4.8).

Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

Dizziness
Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

This medicinal product contains 2.6 mmol (or 59.8 mg) sodium per vial. To be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, eslicarbazepine, pregabalin) and in patients treated with class I antiarrhythmics. However, subgroup analysis did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or

lamotrigine in clinical trials.

In vitro data
Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, 2B6, and 2C9 are not induced and that CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, and 2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data
Lacosomide does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily) but C_{max} of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).
The CYP2C19 inhibitor omeprazole (40 mg q.d.) did not give rise to a clinically significant change in lacosamide exposure. Thus moderate inhibitors of CYP2C19 are unlikely to affect systemic lacosamide exposure to a clinically relevant extent.
Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of lacosamide. Such interactions have not been established *in vivo* but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John´s wort (Hypericum perforatum) may moderately reduce the systemic exposure of lacosamide. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptics
In interaction trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. A population PK analysis estimated that concomitant treatment with other anti-epileptics known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25%.

Oral contraceptives
In an interaction trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others
Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.
Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.
Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.
Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other drugs through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all anti-epileptic drugs, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the

general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.
Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide
There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.
Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding
It is unknown whether lacosamide is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility
No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MRHD).

4.7 Effects on ability to drive and use machines

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.
Accordingly, patients should be advised not to drive a car or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients randomized to lacosamide and 35.2% of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥10%) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.
In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to lacosamide and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.
Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common (≥1/10),

common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (frequency cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[1]
Immune system disorders			Drug hypersensitivity[1]	Drug reaction with eosinophilia and systemic symptoms (DRESS) [1,2]
Psychiatric disorders		Depression Confusional state Insomnia[1]	Aggression[1] Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt [1] Suicidal ideation [1] Hallucination [1]	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope [2]	
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[1,2] Bradycardia[1,2] Atrial Fibrillation [1,2] Atrial Flutter [1,2]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [2] Hepatic enzyme increased (> 2x ULN) [1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema[1] Urticaria[1]	Stevens-Johnson syndrome[1]

				Toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk Injection site pain or discomfort [3] Irritation[3]	Erythema[3]	
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[1] Adverse reactions reported in post marketing experience.
[2] See Description of selected adverse reactions.
[3] Local adverse reactions associated with intravenous administration

Description of selected adverse reactions
The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR interval prolongation (e.g. atrioventricular block, syncope, bradycardia) may occur. In adjunctive clinical trials in epilepsy patients the incidence rate of reported first degree AV Block is uncommon, 0.7%, 0%, 0.5% and 0% for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second or higher degree AV Block was seen in these studies. However, cases with second and third degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.
The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1%) and placebo (n=364) treated epilepsy patients (0.3%). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6%) lacosamide patients and in 1/442 (0.2%) carbamazepine CR patients.
Atrial fibrillation or flutter were not reported in short term clinical trials; however both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥ 3x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients.

Multiorgan hypersensitivity reactions
Multiorgan hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with some antiepileptic agents. These reactions are variable in expression but typically present with fever and rash and can be associated with involvement of different organ systems. If multiorgan hypersensitivity reaction is suspected, lacosamide should be discontinued.

Paediatric Population
Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the types of adverse reactions related to lacosamide in elderly patients (≥ 65 years of age) appear to be similar to that observed in

patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients. The most frequent cardiac-related adverse reaction reported in elderly compared to the younger population was first degree AV block. This was reported with lacosamide in 4.8% (3/62) in elderly patients versus 1.6% (6/382) in younger adult patients. The discontinuation rate due to adverse events observed with lacosamide was 21.0% (13/62) in elderly patients versus 9.2% (35/382) in younger adult patients. These differences between elderly and younger patients were similar to those observed in the active comparator group.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms observed after an accidental or intentional overdose of lacosamide are primarily associated with CNS and gastrointestinal system.

- The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of lacosamide.
- Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalized tonic-clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of lacosamide.

Management
There is no specific antidote for overdose with lacosamide. Treatment of lacosamide overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX18

Mechanism of action
The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.
The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated.
In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects
Lacosamide protected against seizures in a broad range of animal models of partial and primary generalized seizures and delayed kindling development.
In non-clinical experiments lacosamide in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

Clinical efficacy and safety
Monotherapy

Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in 886 patients 16 years of age or older with newly or recently diagnosed epilepsy. The patients had to present with unprovoked partial onset seizures with or without secondary generalization. The patients were randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 1200 mg/day for carbamazepine CR and from 200 to 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.
The estimated 6-month seizure freedom rates were 89.8% for lacosamide-treated patients and 91.1% for carbamazepine CR treated patients using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.3% (95 % CI: -5.5, 2.8). The Kaplan-Meier estimates of 12-month seizure freedom rates were 77.8% for lacosamide-treated patients and 82.7% for carbamazepine CR treated patients.
The 6-month seizure freedom rates in elderly patients of 65 and above (62 patients in lacosamide, 57 patients in carbamazepine CR) were similar between both treatment groups. The rates were also similar to those observed in the overall population. In the elderly population, the maintenance lacosamide dose was 200 mg/day in 55 patients (88.7%), 400 mg/day in 6 patients (9.7%) and the dose was escalated to over 400 mg/day in 1 patient (1.6%).

Conversion to monotherapy
The efficacy and safety of lacosamide in conversion to monotherapy has been assessed in a historical-controlled, multicentre, double-blind, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Adjunctive therapy
The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptics in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

The pharmacokinetics and safety of a single loading dose of iv lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single iv loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the iv dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

5.2 Pharmacokinetic properties

Absorption
After i.v. administration, C_{max} is reached at the end of infusion. The plasma concentration increases proportionally with dose after oral (100-800 mg) and i.v. (50-300 mg) administration.

Distribution
The volume of distribution is approximately 0.6 L/kg. Lacosamide is less than 15% bound to plasma proteins.

Biotransformation
95% of the dose is excreted in the urine as drug and metabolites. The metabolism of lacosamide has not been completely characterised.
The major compounds excreted in urine are unchanged lacosamide (approximately 40% of the dose) and its O-desmethyl metabolite less than 30%.
A polar fraction proposed to be serine derivatives accounted for approximately 20% in urine, but was detected only in small amounts (0-2%) in human plasma of some subjects. Small amounts (0.5-2%) of additional metabolites were found in the urine.

In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*. No clinically relevant difference in lacosamide exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19). Furthermore an interaction trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor.
The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination
Lacosamide is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled lacosamide, approximately 95% of radioactivity administered was recovered in the urine and less than 0.5% in the feces. The elimination half-life of the unchanged drug is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Pharmacokinetics in special patient groups

Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with endstage renal disease requiring hemodialysis compared to healthy subjects, whereas c_{max} was unaffected.
Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50%. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment
Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of lacosamide (approximately 50% higher AUC_{norm}). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20% increase in the AUC of lacosamide. The pharmacokinetics of lacosamide has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age)
In a study in elderly men and women including 4 patients >75 years of age, AUC was about 30 and 50% increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23%, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.
A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

5.3 Preclinical safety data

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.
A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.
In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterise the embryofetotoxic and teratogenic potential of lacosamide.
Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

water for injections
sodium chloride
hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at temperatures up to 25° C for product mixed with the diluents mentioned in 6.6 and stored in glass or PVC bags.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I glass vial with a chlorobutyl rubber closure coated with a fluoropolymer.
Packs of 1x20 ml and 5x20 ml.

Not all packsizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only, any unused solution should be discarded.
Vimpat solution for infusion was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in glass or PVC bags at temperatures up to 25°C.
Diluents:
sodium chloride 9 mg/ml (0.9%) solution for injection
glucose 50 mg/ml (5%) solution for injection
lactated Ringer's solution for injection.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/016-017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 August 2008
Date of latest renewal: 31 July 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Film-coated tablets and solution for infusion

Aesica Pharmaceuticals GmbH Alfred-Nobel Strasse 10 D-40789 Monheim am Rhein Germany	or	UCB Pharma SA Chemin du Foriest B-1420 Braine- l'Alleud Belgium

Syrup

Aesica Pharmaceuticals GmbH
Alfred-Nobel Strasse 10
D-40789 Monheim am Rhein
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

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

An updated RMP should be submitted

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 50 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
168 film-coated tablets
56 x 1 film-coated tablet
14 x 1 film-coated tablet28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/001 14 film-coated tablets
EU/1/08/470/002 56 film-coated tablets
EU/1/08/470/003 168 film-coated tablets
EU/1/08/470/020 56 x 1 film-coated tablet
EU/1/08/470/024 14 x 1 film-coated tablet
EU/1/08/470/025 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 50 mg
<Justification for not including Braille accepted> 56 x 1 and 14 x 1 film-coated tablet

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 100 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
168 film-coated tablets
56 x 1 film-coated tablet
14 x 1 film-coated tablet
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/004 14 film-coated tablets
EU/1/08/470/005 56 film-coated tablets
EU/1/08/470/006 168 film-coated tablets
EU/1/08/470/021 56 x 1 film-coated tablet
EU/1/08/470/026 14 x 1 film-coated tablet
EU/1/08/470/027 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 100 mg
<Justification for not including Braille accepted> 56 x 1 and 14 x 1 film-coated tablet

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 150 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
14 x 1 film-coated tablet
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/007 14 film-coated tablets
EU/1/08/470/008 56 film-coated tablets
EU/1/08/470/022 56 x 1 film-coated tablet
EU/1/08/470/028 14 x 1 film-coated tablet
EU/1/08/470/029 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 150 mg
<Justification for not including Braille accepted> 56 x 1 and 14 x 1 film-coated tablet

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
Carton of 168 film-coated tablets containing 3 Cartons of 56 film-coated tablets (with Blue box)

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 150 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 168 (3 packs of 56) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
Intermediate Carton
Carton of 56 film-coated tablets 150 mg (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 150 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 200 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
56 x 1 film-coated tablet
14 x 1 film-coated tablet
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/010 14 film-coated tablets
EU/1/08/470/011 56 film-coated tablets
EU/1/08/470/023 56 x 1 film-coated tablet
EU/1/08/470/030 14 x 1 film-coated tablet
EU/1/08/470/031 28 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 200 mg
<Justification for not including Braille accepted> 56 x 1 and 14 x 1 film-coated tablet

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
Carton of 168 film-coated tablets containing 3 Cartons of 56 film-coated tablets (with Blue box)

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 200 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 168 (3 packs of 56) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS ONLY
Intermediate Carton
Carton of 56 film-coated tablets 200 mg (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 200 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
TREATMENT INITIATION PACK ONLY

Outer carton - treatment initiation pack containing 4 cartons of 14 film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg
Vimpat 100 mg
Vimpat 150 mg
Vimpat 200 mg
film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Vimpat 50 mg
1 film-coated tablet contains 50 mg lacosamide.
Vimpat 100 mg
1 film-coated tablet contains 100 mg lacosamide.
Vimpat 150 mg
1 film-coated tablet contains 150 mg lacosamide.
Vimpat 200 mg
1 film-coated tablet contains 200 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Treatment initiation pack
Each pack of 56 film-coated tablets for a 4-week treatment schedule contains:
14 film-coated tablets of Vimpat 50 mg
14 film-coated tablets of Vimpat 100 mg
14 film-coated tablets of Vimpat 150 mg
14 film-coated tablets of Vimpat 200 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 50 mg
Vimpat 100 mg
Vimpat 150 mg
Vimpat 200 mg

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate Carton
Carton 14 tablets – week 1

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 50 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets.
Week 1

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 50 mg

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label – week 1

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 1

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate Carton
Carton 14 tablets – week 2

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 100 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets.
Week 2

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 100 mg

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label – week 2

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 2

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate Carton
Carton 14 tablets – week 3

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 150 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets.
Week 3

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 150 mg

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label – week 3

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 3

TREATMENT INITIATION PACK ONLY
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Intermediate Carton
Carton 14 tablets – week 4

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 200 mg lacosamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets.
Week 4

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 200 mg

TREATMENT INITIATION PACK ONLY
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label – week 4

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
Lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 4

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton / bottle

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 10 mg/ml syrup
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of syrup contains 10 mg lacosamide.
1 bottle of 200 ml contains 2000 mg lacosamide
1 bottle of 465 ml contains 4650 mg lacosamide

3. LIST OF EXCIPIENTS

Contains sorbitol (E420), sodium methyl parahydroxybenzoate (E219) and aspartame (E951), sodium.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

200 ml syrup with measuring cup
465 ml syrup with measuring cup

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. *(only for the outer carton)*
Oral use.
Shake well before use
Only use the measuring cup within this pack

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, bottle may be used for up to 4 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/018
EU/1/08/470/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vimpat 10 mg/ml *(only for the outer carton)*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 10 mg/ml solution for infusion
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 10 mg lacosamide.
1 vial of 20 ml contains 200 mg lacosamide

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, hydrochloric acid, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

1x20 ml solution for infusion
200 mg/20 ml
5x20 ml solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/016
EU/1/08/470/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 10 mg/ml solution for infusion
Lacosamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 10 mg lacosamide.
1 vial of 20 ml contains 200 mg lacosamide

3. LIST OF EXCIPIENTS

Sodium chloride, hydrochloric acid, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

200 mg/20ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
IV use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vimpat 50 mg film-coated tablets
Vimpat 100 mg film-coated tablets
Vimpat 150 mg film-coated tablets
Vimpat 200 mg film-coated tablets
Lacosamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vimpat is and what it is used for
2. What you need to know before you take Vimpat
3. How to take Vimpat
4. Possible side effects
5. How to store Vimpat
6. Contents of the pack and other information

1. What Vimpat is and what it is used for

Lacosamide (Vimpat) is used to treat a certain form of epilepsy (see below) in patients aged 16 years and older.
Epilepsy is a condition where the patients have repeated fits (seizures). Vimpat is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation).
Vimpat has been given to you by your doctor to reduce the number of fits.
Vimpat may be used on its own or with other antiepileptic medicines.

2. What you need to know before you take Vimpat

Do not take Vimpat
- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in Section 6). If you are not sure whether you are allergic, please discuss with your doctor
- if you suffer from a certain type of heart rhythm disorder (second or third degree AV block)

Warnings and precautions
A small number of people being treated with anti-epileptics such as lacosamide have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor before taking Vimpat if you suffer from a condition that is associated with impaired electric conduction across the heart (AV block, atrial fibrillation and atrial flutter) or from severe heart disease such as, heart failure or heart attack. Symptoms of AV block are slow or irregular pulse, feeling of lightheaded and fainting. In case of atrial fibrillation and flutter you may experience palpitations, rapid or irregular pulse and shorteness of breath.

Vimpat may cause dizziness, which could increase the risk of accidental injury or a fall. Therefore, you should be careful until you are used to the effects this medicine might have.

Children and adolescents
Vimpat is not recommended for children and adolescents aged under 16 years. The safety and efficacy are not yet known in this age group.

Other medicines and Vimpat
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you take medicines to treat heart problems or if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval including carbamazepine, lamotrigine, pregabalin (medicines used to treat epilepsy) and medicines used to treat certain types of irregular heart beat or heart failure. If you are not sure if the medicines you are taking could have this effect, discuss this with your doctor.
Medicines such as fluconazole, itraconazole, ketoconazole (medicines used to treat fungal infections), ritonavir (a medicine used to treat HIV infection), clarithromycin, rifampicin (medicines used to treat bacterial infections) and St.John's wort (a medicine used to treat mild anxiety) could affect how the liver breaks down lacosamide.

Vimpat with alcohol
As a safety precaution do not take Vimpat with alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not recommended to take Vimpat if you are pregnant, as the effects of Vimpat on pregnancy and the unborn baby are not known. Tell your doctor immediately if you are pregnant or planning to become pregnant; he/she will decide if you should take Vimpat.

It is not recommended to breast-feed your baby while taking Vimpat, as it is not known if Vimpat passes into the breast milk. If you are breast-feeding, please inform your doctor immediately; he/she will decide if you should take Vimpat.

Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. On the other hand effective anti-epileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Driving and using machines
Vimpat may cause dizziness or blurred vision. This may affect your ability to drive or operate any tools or machinery. You should not drive or use machines until you know whether this medicine affects your ability to perform these activities.

3. How to take Vimpat

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Administration of a loading dose has not been studied in patients with status epilepticus.

<u>Dosage</u>
Vimpat must be taken twice a day, once in the morning and once in the evening, at about the same time each day. Vimpat is used as a long term treatment.

When you take Vimpat on its own:
The usual starting dose of Vimpat is 100 mg per day, taken in 2 divided doses of 50 mg in the morning and 50 mg in the evening.
Your doctor may also prescribe a starting dose of 200mg of Vimpat per day, taken in 2 divided doses of 100 mg in the morning and 100 mg in the evening.

Your doctor may increase your daily dose every week by 100 mg, until you reach a so called maintenance dose between 200 mg and 600 mg per day, taken in 2 divided doses. You will use this maintenance dose for the long term treatment.

When you take Vimpat with other antiepileptic medicines:
The usual starting dose of Vimpat is 100 mg per day, taken in 2 divided doses of 50 mg in the morning and 50 mg in the evening. Your doctor may increase your daily dose every week by 100 mg, until you reach a so called maintenance dose between 200 mg and 400 mg per day, taken in 2 divided doses. You will use this maintenance dose for the long term treatment.

Your doctor may decide to initiate Vimpat treatment with a single loading dose of 200 mg followed approximately 12 hours later by initiation of a maintenance dose regimen. A loading dose should be administered under medical supervision.

Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

How to take the Vimpat tablets
You should swallow the Vimpat tablet with a glass of water. You may take Vimpat with or without food.

Duration of the treatment with Vimpat
Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately.
You may experience dizziness, nausea, vomiting, seizures, heart complaints, coma or a fall in blood pressure with rapid heartbeat and sweating.
Do not try to drive.

If you forget to take Vimpat
If you miss a dose by a few hours, take it as soon as you remember. If it is close (less than 6 hours) to your next dose, don't take the missed tablet anymore. Just take Vimpat at the next time that you would normally take it. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vimpat
Do not stop taking Vimpat without talking to your doctor, as your symptoms may come back again or become worse.
If your doctor decides to stop your treatment with Vimpat, he/she will instruct you about how you should decrease the dose step by step.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Nervous system side effects such as dizziness may be higher after a loading dose.

Very common: may affect more than 1 in 10 people
- Dizziness, headache
- Nausea (feeling sick)
- Double vision (diplopia)

Common: may affect up to 1 in 10 people
- Problems in keeping your balance, difficulties in coordinating your movements, troubles with

your memory, sleepiness, shaking (tremor), trouble thinking or finding words, rapid and uncontrollable movements of the eyes (nystagmus), tingling (paresthesia)
- Blurred vision
- A feeling of "spinning" (vertigo)
- Vomiting, constipation, excessive gas in the stomach or bowel, diarrhoea
- Itching
- Fall, bruise
- Tiredness, difficulties in walking, unusual tiredness and weakness (asthenia), feeling drunk
- Depression
- Confusion
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention
- Noise in the ear such as buzzing, ringing or whistling
- Indigestion, dry mouth
- Irritability
- Muscle spasms
- Rash
- Trouble sleeping

Uncommon: may affect up to 1 in 100 people
- Slow heart rate
- Heart conduction disorder
- Exaggerated feeling of wellbeing
- Allergic reaction to drug intake
- Liver function test abnormal, liver injury
- Attempt to commit suicide
- Thoughts about suicide or hurting yourself
- Palpitations and/or rapid or irregular pulse
- Aggression
- Agitation
- Abnormal thinking and/or loss of touch with reality
- Serious allergic reaction which causes swelling of the face, throat, hand, feet, ankles, or lower legs
- Hives
- Hallucinations (Seeing and/or hearing things that are not real)
- Fainting

Not known: frequency cannot be estimated from available data
- Severe decrease in a specific class of white blood cells (agranulocytosis)
- Serious skin reaction which may include flu-like symptoms, a rash on the face, extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes
- A widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens–Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vimpat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vimpat contains
The active substance is lacosamide.
One tablet of Vimpat 50 mg contains 50 mg lacosamide.
One tablet of Vimpat 100 mg contains 100 mg lacosamide.
One tablet of Vimpat 150 mg contains 150 mg lacosamide.
One tablet of Vimpat 200 mg contains 200 mg lacosamide.

The other ingredients are:
Tablet core: microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylcellulose (low substituted), colloidal anhydrous silica, crospovidone (polyplasdone XL-10 Pharmaceutical Grade), magnesium stearate
Film-coat: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), colourants*
***** The colourants are:
50 mg tablet: red iron oxide (E172), black iron oxide (E172), indigo carmine aluminium lake (E132)
100 mg tablet: yellow iron oxide (E172)
150 mg tablet: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)
200 mg tablet: indigo carmine aluminium lake (E132)

What Vimpat looks like and contents of the pack
Vimpat 50 mg are pinkish, oval film-coated tablets with a debossed ‘SP’ on one side and ‘50’ on the other side.
Vimpat 100 mg are dark yellow, oval film-coated tablets with a debossed ‘SP’ on one side and ‘100’ on the other side.
Vimpat 150 mg are salmon, oval film-coated tablets with a debossed ‘SP’ on one side and ‘150’ on the other side.
Vimpat 200 mg are blue, oval film-coated tablets with a debossed ‘SP’ on one side and ‘200’ on the other side.

Vimpat is available in packs of 14, 28, 56, 14 x 1 and 56 x 1 film-coated tablets and in multipacks comprising 3 cartons, each containing 56 tablets. The 14 x 1 and 56 x 1 film-coated tablet packs are available as perforated unit dose PVC/PVDC blisters sealed with an aluminium foil, all other packs are available with standard PVC/PVDC blisters sealed with an aluminium foil. Not all pack sizes may be marketed.

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Manufacturer
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or
Aesica Pharmaceuticals GmbH, Alfred-Nobel Strasse 10, D-40789 Monheim am Rhein, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {month/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the patient

Vimpat 50 mg film-coated tablets
Vimpat 100 mg film-coated tablets
Vimpat 150 mg film-coated tablets
Vimpat 200 mg film-coated tablets
Lacosamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in the leaflet. See section 4.

What is in this leaflet

1. What Vimpat is and what it is used for
2. What you need to know before you take Vimpat
3. How to take Vimpat
4. Possible side effects
5. How to store Vimpat
6. Contents of the pack and other information

1. What Vimpat is and what it is used for

Lacosamide (Vimpat) is used to treat a certain form of epilepsy (see below) in patients aged 16 years and older.
Epilepsy is a condition where the patients have repeated fits (seizures). Vimpat is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation).
Vimpat has been given to you by your doctor to reduce the number of fits.
Vimpat may be used on its own or with other antiepileptic medicines.

2. What you need to know before you take Vimpat

Do not take Vimpat
- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in Section 6). If you are not sure whether you are allergic, please discuss with your doctor
- if you suffer from a certain type of heart rhythm disorder (second or third degree AV block)

Warnings and precautions
A small number of people being treated with anti-epileptics such as lacosamide have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor before taking Vimpat if you suffer from a condition that is associated with impaired electric conduction across the heart (AV block, atrial fibrillation and atrial flutter)or from severe heart disease such as, heart failure or heart attack. Symptoms of AV block are slow or irregular pulse, feeling of lightheaded and fainting. In case of atrial fibrillation and flutter you may experience palpitations, rapid or irregular pulse and shortness of breath.

Vimpat may cause dizziness, which could increase the risk of accidental injury or a fall. Therefore, you should be careful until you are used to the effects this medicine might have.

Children and adolescents
Vimpat is not recommended for children and adolescents aged under 16 years. The safety and efficacy are not yet known in this age group.

Other medicines and Vimpat
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you take medicines to treat heart problems or if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval including carbamazepine, lamotrigine, pregabalin (medicines used to treat epilepsy) and medicines used to treat certain types of irregular heart beat or heart failure. If you are not sure if the medicines you are taking could have this effect, discuss this with your doctor.
Medicines such as fluconazole, itraconazole, ketoconazole (medicines used to treat fungal infections), ritonavir (a medicine used to treat HIV infection), clarithromycin, rifampicin (medicines used to treat bacterial infections) and St.John's wort (a medicine used to treat mild anxiety) could affect how the liver breaks down lacosamide.

Vimpat with alcohol
As a safety precaution do not take Vimpat with alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby ask your doctor or pharmacist for advice before taking this medicine.

It is not recommended to take Vimpat if you are pregnant, as the effects of Vimpat on pregnancy and the unborn baby are not known. Tell your doctor immediately if you are pregnant or planning to become pregnant; he/she will decide if you should take Vimpat.

It is not recommended to breast-feed your baby while taking Vimpat, as it is not known if Vimpat passes into the breast milk. If you are breast-feeding, please inform your doctor immediately; he/she will decide if you should take Vimpat.

Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. On the other hand effective anti-epileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Driving and using machines
Vimpat may cause dizziness or blurred vision. This may affect your ability to drive or operate any tools or machinery. You should not drive or use machines until you know whether this medicine affects your ability to perform these activities.

3. How to take Vimpat

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

<u>Dosage</u>
Vimpat must be taken twice a day, once in the morning and once in the evening, at about the same time each day. Vimpat is used as a long term treatment.

When you take Vimpat on its own:
The usual starting dose of Vimpat is 100 mg per day, taken in 2 divided doses of 50 mg in the morning and 50 mg in the evening.
Your doctor may also prescribe a starting dose of 200mg of Vimpat per day, taken in 2 divided doses of 100 mg in the morning and 100 mg in the evening.

Your doctor may increase your daily dose every week by 100 mg, until you reach a so called maintenance dose between 200 mg and 600 mg per day, taken in 2 divided doses. You will use this maintenance dose for the long term treatment.

When you take Vimpat with other antiepileptic medicines:
Start of the treatment (the first 4 weeks)
This pack (treatment initiation pack) is used when you start your treatment with Vimpat.
The pack contains 4 different packages for the first 4 weeks of treatment, one package for each week.
Each package has 14 tablets, corresponding to 2 tablets per day for 7 days.
Each package contains a different dosage strength of Vimpat, so you will increase your dose gradually.
You will start your treatment with a low dose of Vimpat, usually 50 mg twice a day, and increase it week by week. The usual dose that may be taken per day for each of the first 4 weeks of treatment is shown in the following table. Your doctor will tell you whether you need all 4 packages.

Table: Start of the treatment (the first 4 weeks)

Week	**Package to be used**	**First dose (in the morning)**	**Second dose (in the evening)**	**TOTAL daily dose**
Week 1	Package marked "Week 1"	50 mg (1tablet Vimpat 50 mg)	50 mg (1 tablet Vimpat 50 mg)	100 mg
Week 2	Package marked "Week 2"	100 mg (1 tablet Vimpat 100 mg)	100 mg (1 tablet Vimpat 100 mg)	200 mg
Week 3	Package marked "Week 3"	150 mg (1 tablet Vimpat 150 mg)	150 mg (1 tablet Vimpat 150 mg)	300 mg
Week 4	Package marked "Week 4"	200 mg (1 tablet Vimpat 200 mg)	200 mg (1 tablet Vimpat 200 mg)	400 mg

Maintenance treatment (after the first 4 weeks)
After the first 4 weeks of treatment, your doctor may adjust the dose with which you will continue your long term treatment. This dose is called a maintenance dose and will depend on how you respond to Vimpat. For most patients the maintenance dose is between 200 mg and 400 mg per day.

Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

How to take the Vimpat tablets
You should swallow the Vimpat tablet with a glass of water. You may take Vimpat with or without food.

Duration of the treatment with Vimpat
Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately.
You may experience dizziness, nausea, vomiting, seizures, heart complaints, coma or a fall in blood pressure with rapid heartbeat and sweating.
Do not try to drive.

If you forget to take Vimpat
If you miss a dose by a few hours, take it as soon as you remember. If it is close (less than 6 hours) to your next dose, don't take the missed tablet anymore. Just take Vimpat at the next time that you would normally take it. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vimpat
Do not stop taking Vimpat without talking to your doctor, as your symptoms may come back again or become worse.
If your doctor decides to stop your treatment with Vimpat, he/she will instruct you about how you should decrease the dose step by step.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people
- Dizziness, headache
- Nausea (feeling sick)
- Double vision (diplopia)

Common: may affect up to 1 in 10 people
- Problems in keeping your balance, difficulties in coordinating your movements, troubles with your memory, sleepiness, shaking (tremor), trouble thinking or finding words, rapid and uncontrollable movements of the eyes (nystagmus), tingling (paresthesia)
- Blurred vision
- A feeling of "spinning" (vertigo)
- Vomiting, constipation, excessive gas in the stomach or bowel, diarrhoea
- Itching
- Fall, bruise
- Tiredness, difficulties in walking, unusual tiredness and weakness (asthenia), feeling drunk
- Depression
- Confusion
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention
- Noise in the ear such as buzzing, ringing or whistling
- Indigestion, dry mouth
- Irritability
- Muscle spasms
- Rash
- Trouble sleeping

Uncommon: may affect up to 1 in 100 people
- Slow heart rate
- Heart conduction disorder
- Exaggerated feeling of wellbeing
- Allergic reaction to drug intake
- Liver function test abnormal, liver injury
- Attempt to commit suicide
- Thoughts about suicide or hurting yourself
- Palpitations and/or rapid or irregular pulse
- Aggression
- Agitation
- Abnormal thinking and/or loss of touch with reality
- Serious allergic reaction which causes swelling of the face, throat, hand, feet, ankles, or lower legs
- Hives
- Hallucinations (Seeing and/or hearing things that are not real)
- Fainting

Not known: frequency cannot be estimated from available data

- Severe decrease in a specific class of white blood cells (agranulocytosis)
- Serious skin reaction which may include flu-like symptoms, a rash on the face, extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes
- A widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens–Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vimpat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vimpat contains
The active substance is lacosamide.
One tablet of Vimpat 50 mg contains 50 mg lacosamide.
One tablet of Vimpat 100 mg contains 100 mg lacosamide.
One tablet of Vimpat 150 mg contains 150 mg lacosamide.
One tablet of Vimpat 200 mg contains 200 mg lacosamide.

The other ingredients are:
Tablet core: microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylcellulose (low substituted), colloidal anhydrous silica, crospovidone (polyplasdone XL-10 Pharmaceutical Grade), magnesium stearate
Film-coat: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), colourants*
***** The colourants are:
50 mg tablet: red iron oxide (E172), black iron oxide (E172), indigo carmine aluminium lake (E132)
100 mg tablet: yellow iron oxide (E172)
150 mg tablet: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)
200 mg tablet: indigo carmine aluminium lake (E132)

What Vimpat looks like and contents of the pack
Vimpat 50 mg are pinkish, oval film-coated tablets with a debossed ‘SP’ on one side and ‘50’ on the other side.
Vimpat 100 mg are dark yellow, oval film-coated tablets with a debossed ‘SP’ on one side and ‘100’ on the other side.
Vimpat 150 mg are salmon, oval film-coated tablets with a debossed ‘SP’ on one side and ‘150’ on the other side.

Vimpat 200 mg are blue, oval film-coated tablets with a debossed ‘SP’ on one side and ‘200’ on the other side.

The treatment initiation pack contains 56 film-coated tablets in 4 packages:
- the package marked ‘Week 1’contains 14 tablets of 50 mg,
- the package marked ‘Week 2’ contains 14 tablets of 100 mg,
- the package marked ‘Week 3’ contains 14 tablets of 150 mg,
- the package marked ‘Week 4’ contains 14 tablets of 200 mg .

Marketing Authorisation Holder
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or
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {month/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Package leaflet: Information for the patient

Vimpat 10 mg/ml syrup
Lacosamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of ilness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vimpat is and what it is used for
2. What you need to know before you take Vimpat
3. How to take Vimpat
4. Possible side effects
5. How to store Vimpat
6. Contents of the pack and other information

1. What Vimpat is and what it is used for

Lacosamide (Vimpat) is used to treat a certain form of epilepsy (see below) in patients aged 16 years and older.
Epilepsy is a condition where the patients have repeated fits (seizures). Vimpat is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation).
Vimpat has been given to you by your doctor to reduce the number of fits.
Vimpat may be used on its own or with other antiepileptic medicines.

2. What you need to know before you take Vimpat

Do not take Vimpat
- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in Section 6). If you are not sure whether you are allergic, please discuss with your doctor
- if you suffer from a certain type of heart rhythm disorder (second or third degree AV block)

Warnings and precautions
A small number of people being treated with anti-epileptics such as lacosamide have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor before taking Vimpat if you suffer from a condition that is associated with impaired electric conduction across the heart (AV block, atrial fibrillation and atrial flutter) or from severe heart disease such as, heart failure or heart attack. Symptoms of AV block are slow or irregular pulse, feeling of lightheaded and fainting. In case of atrial fibrillation and flutter you may experience palpitations, rapid or irregular pulse and shortness of breath.

Vimpat may cause dizziness, which could increase the risk of accidental injury or a fall. Therefore, you should be careful until you are used to the effects this medicine might have.

Children and adolescents

Vimpat is not recommended for children and adolescents aged under 16 years. The safety and efficacy are not yet known in this age group.

Other medicines and Vimpat
Tell your doctor or pharmacist if you are taking have recently taken or might take any other medicines. This is especially important if you take medicines to treat heart problems or if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval including carbamazepine, lamotrigine, pregabalin (medicines used to treat epilepsy) and medicines used to treat certain types of irregular heart beat or heart failure. If you are not sure if the medicines you are taking could have this effect, discuss this with your doctor.
Medicines such as fluconazole, itraconazole, ketoconazole (medicines used to treat fungal infections), ritonavir (a medicine used to treat HIV infection), clarithromycin, rifampicin (medicines used to treat bacterial infections) and St.John's wort (a medicine used to treat mild anxiety) could affect how the liver breaks down lacosamide.

Vimpat with alcohol
As a safety precaution do not take Vimpat with alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby ask your doctor or pharmacist for advice before taking this medicine.

It is not recommended to take Vimpat if you are pregnant, as the effects of Vimpat on pregnancy and the unborn baby are not known. Tell your doctor immediately if you are pregnant or planning to become pregnant; he/she will decide if you should take Vimpat.

It is not recommended to breast-feed your baby while taking Vimpat, as it is not known if Vimpat passes into the breast milk. If you are breast-feeding, please inform your doctor immediately; he/she will decide if you should take Vimpat.

Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. On the other hand effective anti-epileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Driving and using machines
Vimpat may cause dizziness or blurred vision. This may affect your ability to drive or operate any tools or machinery. You should not drive or use machines until you know whether this medicine affects your ability to perform these activities.

Vimpat contains sorbitol, sodium, sodium methyl parahydroxybenzoate and aspartame
Vimpat syrup contains:
- sorbitol (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- sodium. One graduation mark of syrup contains 0.31 mmol (or 7.09 mg) sodium. If you take more than 3 graduation marks of syrup per day and are on a controlled sodium diet, you should take into consideration the amount of sodium in the syrup.
- one ingredient called sodium methyl parahydroxybenzoate-E219 which may cause allergic reactions (possibly delayed).
- aspartame (E951), a source of phenylalanine. This substance may be harmful for people with phenylketonuria (a metabolic disease).

3. How to take Vimpat

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Administration of a loading dose has not been studied in patients with status epilepticus.

Dosage
Vimpat must be taken twice a day, once in the morning and once in the evening, at about the same time each day. Vimpat is used as a long term treatment.

When you take Vimpat on its own:
The usual starting dose of Vimpat is 100 mg per day, taken in 2 divided doses of 50 mg (5ml) in the morning and 50 mg (5ml) in the evening.
Your doctor may also prescribe a starting dose of 200mg of Vimpat per day, taken in 2 divided doses of 100 mg (10ml) in the morning and 100 mg (10ml) in the evening.
Your doctor may increase your daily dose every week by 100 mg, until you reach a so called maintenance dose between 200 mg and 600 mg per day, taken in 2 divided doses. You will use this maintenance dose for the long term treatment.

When you take Vimpat with other antiepileptic medicines:
The usual starting dose of Vimpat is 100 mg per day, taken in 2 divided doses of 50 mg (5ml) in the morning and 50 mg (5ml) in the evening.
Your doctor may increase your daily dose every week by 100 mg, until you reach a so called maintenance dose between 200 mg and 400 mg per day, taken in 2 divided doses. You will use this maintenance dose for the long term treatment.

Your doctor may decide to initiate Vimpat treatment with a single loading dose of 200 mg followed approximately 12 hours later by initiation of a maintenance dose regimen. A loading dose should be administered under medical supervision.

Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

How to take the Vimpat syrup
Shake the bottle well before use. ***Use only the measuring cup within this pack.***
Fill the measuring cup to the graduation mark(s) corresponding to your prescribed dose.
Each graduation mark (5ml) of the measuring cup corresponds to 50 mg (for example 2 graduation marks correspond to 100 mg).
Swallow the dose of syrup, then drink some water. You may take Vimpat with or without food.

Duration of the treatment with Vimpat
Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

Once you have opened the syrup bottle, you must not use it longer than 4 weeks.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately.
You may experience dizziness, nausea, vomiting, seizures, heart complaints, coma or a fall in blood pressure with rapid heartbeat and sweating.
Do not try to drive.

If you forget to take Vimpat
If you miss a dose by a few hours, take it as soon as you remember. If it is close (less than 6 hours) to your next dose, don't take the missed syrup anymore. Just take Vimpat at the next time that you would normally take it. Do not take a double dose to make up for a forgotten dose.

If you stop taking Vimpat
Do not stop taking Vimpat without talking to your doctor, as your symptoms may come back again or become worse.
If your doctor decides to stop your treatment with Vimpat, he/she will instruct you about how you should decrease the dose step by step.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Nervous system side effects such as dizziness may be higher after a loading dose.

Very common: may affect more than 1 in 10 people
- Dizziness, headache
- Nausea (feeling sick)
- Double vision (diplopia)

Common: may affect up to 1 in 10 people
- Problems in keeping your balance, difficulties in coordinating your movements, troubles with your memory, sleepiness, shaking (tremor), trouble thinking or finding words, rapid and uncontrollable movements of the eyes (nystagmus), tingling (paresthesia)
- Blurred vision
- A feeling of "spinning" (vertigo)
- Vomiting, constipation, excessive gas in the stomach or bowel, diarrhoea
- Itching
- Fall, bruise
- Tiredness, difficulties in walking, unusual tiredness and weakness (asthenia), feeling drunk
- Depression
- Confusion
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention
- Noise in the ear such as buzzing, ringing or whistling
- Indigestion, dry mouth
- Irritability
- Muscle spasms
- Rash
- Trouble sleeping

Uncommon: may affect up to 1 in 100 people
- Slow heart rate
- Heart conduction disorder
- Exaggerated feeling of wellbeing
- Allergic reaction to drug intake
- Liver function test abnormal, liver injury
- Attempt to commit suicide
- Thoughts about suicide or hurting yourself
- Palpitations and/or rapid or irregular pulse
- Aggression
- Agitation
- Abnormal thinking and/or loss of touch with reality
- Serious allergic reaction which causes swelling of the face, throat, hand, feet, ankles, or lower legs
- Hives
- Hallucinations (Seeing and/or hearing things that are not real)
- Fainting

Not known: frequency cannot be estimated from available data
- Severe decrease in a specific class of white blood cells (agranulocytosis)

- Serious skin reaction which may include flu-like symptoms, a rash on the face, extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes
- A widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens–Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vimpat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Do not refrigerate.
Once you have opened the syrup bottle, you must not use it longer than 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use . These measures will help protect the environment.

6. Contents of the pack and other information

What Vimpat contains
The active substance is lacosamide.
1 ml Vimpat syrup contains 10 mg lacosamide.

The other ingredients are: glycerol (E422), carmellose sodium, sorbitol liquid (crystallizing) (E420), Polyethylene glycol 4000, sodium chloride, citiric acid, anhydrous, acesulfame potassium (E950), sodium methyl parahydroxybenzoate (E219), strawberry flavour (contains propylene glycol, maltol), masking flavour (contains propylene glycol, aspartame (E951), acesulfame potassium (E950), maltol deionised water), purified water.

What Vimpat looks like and contents of the pack
Vimpat 10 mg/ml syrup is a slightly viscous clear, colourless to yellow-brown liquid.
Vimpat is available in bottles of 200 ml and 465 ml.
Not all pack sizes may be marketed.
A measuring cup with graduation marks (corresponding to 50 mg lacosamide) is provided with the syrup.

Marketing Authorisation Holder
UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium.

Manufacturer
Aesica Pharmaceuticals GmbH, Alfred-Nobel Strasse 10, D-40789 Monheim am Rhein, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {month/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

Package leaflet: Information for the patient

Vimpat 10 mg/ml solution for infusion
Lacosamide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you..
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vimpat is and what it is used for
2. What you need to know before you use Vimpat
3. How to use Vimpat
4. Possible side effects
5. How to store Vimpat
6. Contents of the pack and other information

1. What Vimpat is and what it is used for

Lacosamide (Vimpat) is used to treat a certain form of epilepsy (see below) in patients aged 16 years and older.
Epilepsy is a condition where the patients have repeated fits (seizures). Vimpat is used for the epilepsy form in which the fits initially affect only one side of the brain, but could thereafter extend to larger areas on both sides of the brain (partial onset seizure with or without secondary generalisation).
Vimpat has been given to you by your doctor to reduce the number of fits.
Vimpat may be used on its own or with other antiepileptic medicines.

2. What you need to know before you use Vimpat

Do not use Vimpat
- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in Section 6). If you are not sure whether you are allergic, please discuss with your doctor
- if you suffer from a certain type of heart rhythm disorder (second or third degree AV block)

Warning and precautions
A small number of people being treated with anti-epileptics such as lacosamide have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor before taking Vimpat if you suffer from a condition that is associated with impaired electric conduction across the heart (AV block, atrial fibrillation and atrial flutter) or from severe heart disease such as, heart failure or heart attack. Symptoms of AV block are slow or irregular pulse, feeling of lightheaded and fainting. In case of atrial fibrillation and flutter you may experience palpitations, rapid or irregular pulse and shortness of breath.

Vimpat may cause dizziness, which could increase the risk of accidental injury or a fall. Therefore, you should be careful until you are used to the effects this medicine might have.

Children and adolescents
Vimpat is not recommended for children and adolescents aged under 16 years. The safety and efficacy are not yet known in this age group.

Other medicines and Vimpat
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines
This is especially important if you take medicines to treat heart problems or if you are taking any medicine which can cause an abnormality on the ECG (electrocardiogram) called increased PR interval including carbamazepine, lamotrigine, pregabalin (medicines used to treat epilepsy) and medicines used to treat certain types of irregular heart beat or heart failure. If you are not sure if the medicines you are taking could have this effect, discuss this with your doctor.
Medicines such as fluconazole, itraconazole, ketoconazole (medicines used to treat fungal infections), ritonavir (a medicine used to treat HIV infection), clarithromycin, rifampicin (medicines used to treat bacterial infections) and St.John's wort (a medicine used to treat mild anxiety) could affect how the liver breaks down lacosamide.

Vimpat with alcohol
As a safety precaution do not take Vimpat with alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby ask your doctor or pharmacist for advice before taking this medicine.

It is not recommended to take Vimpat if you are pregnant, as the effects of Vimpat on pregnancy and the unborn baby are not known. Tell your doctor immediately if you are pregnant or planning to become pregnant; he/she will decide if you should take Vimpat.

It is not recommended to breast-feed your baby while taking Vimpat, as it is not known if Vimpat passes into the breast milk. If you are breast-feeding, please inform your doctor immediately; he/she will decide if you should take Vimpat.

Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. On the other hand effective anti-epileptic therapy must not be interrupted since the worsening of the disease is harmful to both the mother and the unborn child.

Driving and using machines
Vimpat may cause dizziness or blurred vision. This may affect your ability to drive or operate any tools or machinery. You should not drive or use machines until you know whether this medicine affects your ability to perform these activities.

Vimpat contains sodium
This medicinal product contains 2.6 mmol (or 59.8 mg) sodium per vial. To be taken into consideration for patients on a controlled sodium diet.

3. How to use Vimpat
Vimpat therapy can be initiated with either oral or i.v. administration.
The solution for infusion is an alternative form of treatment for a short period of time, when Vimpat can't be taken by mouth. It will be administered into a vein by a health care professional.
It is possible to switch directly from oral administration to infusion and the other way around.
Your total daily dose and frequency of administration remain the same.
Administration of a loading dose has not been studied in patients with status epilepticus

<u>Dosage</u>
Vimpat must be administered twice a day, once in the morning and once in the evening, at about the same time each day.

When you take Vimpat on its own:
The treatment with Vimpat starts usually with a dose of 100 mg daily given half (50 mg) in the morning and half (50 mg) in the evening. The treatment with Vimpat may also start with a dose of

200 mg daily given half (100 mg) in the morning and half (100 mg) in the evening.The daily maintenance dose is between 200 mg and 600 mg.

When you take Vimpat with other antiepileptic medicines:
The treatment with Vimpat starts usually with a dose of 100 mg daily given half (50 mg) in the morning and half (50 mg) in the evening. The daily maintenance dose is between 200 mg and 400 mg.

Your doctor may decide to initiate Vimpat treatment with a single loading dose of 200 mg followed approximately 12 hours later by initiation of a maintenance dose regimen. A loading dose should be administered under medical supervision.

Your doctor may use a different dose if you have problems with your kidneys or with your liver.

How Vimpat is given to you
Vimpat is administered as an infusion into a vein (intravenously) by a healthcare professional. It is infused over 15-60 minutes.

Duration of the treatment with Vimpat solution for infusion
Your doctor will decide for how many days you will receive the infusions. There is experience with twice daily infusions of Vimpat up to 5 days. For the long term treatment Vimpat tablets and syrup are available.

If you stop using Vimpat
If your doctor decides to stop your treatment with Vimpat, he/she will decrease the dose step by step. This is to prevent your symptoms from coming back again or becoming worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Nervous system side effects such as dizziness may be higher after a loading dose.

Very common: may affect more than 1 in 10 people
- Dizziness, headache
- Nausea (feeling sick)
- Double vision (diplopia)

Common: may affect up to 1 in 10 people
- Problems in keeping your balance, difficulties in coordinating your movements, troubles with your memory, sleepiness, shaking (tremor), trouble thinking or finding words, rapid and uncontrollable movements of the eyes (nystagmus), tingling (paresthesia)
- Blurred vision
- A feeling of "spinning" (vertigo)
- Vomiting, constipation, excessive gas in the stomach or bowel, diarrhoea
- Itching
- Fall, bruise
- Tiredness, difficulties in walking, unusual tiredness and weakness (asthenia), feeling drunk
- Depression
- Confusion
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention
- Noise in the ear such as buzzing, ringing or whistling
- Indigestion, dry mouth
- Irritability

- Muscle spasms
- Rash
- Trouble sleeping

Uncommon: may affect up to 1 in 100 people
- Slow heart rate
- Heart conduction disorder
- Exaggerated feeling of wellbeing
- Allergic reaction to drug intake
- Liver function test abnormal, liver injury
- Attempt to commit suicide
- Thoughts about suicide or hurting yourself
- Palpitations and/or rapid or irregular pulse
- Aggression
- Agitation
- Abnormal thinking and/or loss of touch with reality
- Serious allergic reaction which causes swelling of the face, throat, hand, feet, ankles, or lower legs
- Hives
- Hallucinations (Seeing and/or hearing things that are not real)
- Fainting

Not known: frequency cannot be estimated from available data
- Severe decrease in a specific class of white blood cells (agranulocytosis)
- Serious skin reaction which may include flu-like symptoms, a rash on the face, extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes
- A widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens–Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis)

Intravenous administration
Intravenous administration was associated with local side effects such as :

Common: may affect up to 1 in 10 people
- Injection site pain or discomfort,
- Irritation

Uncommon: may affect up to 1 in 100 people
- Redness.

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist.This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vimpat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Each vial of Vimpat solution for infusion must be used only once (single use). Any unused solution should be discarded.

Only clear solution free from particles and discoloration should be used.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vimpat contains
The active substance is lacosamide.
1 ml Vimpat solution for infusion contains 10 mg lacosamide.
1 vial contains 20 ml Vimpat solution for infusion equivalent to 200 mg lacosamide.

The other ingredients are: sodium chloride, hydrochloric acid, water for injection.

What Vimpat looks like and contents of the pack
Vimpat 10 mg/ml solution for infusion is a clear, colourless solution.
Vimpat solution for infusion is available in packages of 1 vial and 5 vials. Each vial contains 20 ml.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium.

Manufacturer
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or
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

The following information is intended for medical or healthcare professionals only

Each vial of Vimpat solution for infusion must be used only once (single use). Any unused solution should be discarded (see section 3).

Vimpat solution for infusion can be administered without further dilution, or may be diluted with the following solutions: sodium chloride 9 mg/ml (0.9%), glucose 50 mg/ml (5%) or lactated Ringer's solution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at temperatures up to 25° C for product mixed with these diluents and stored in glass or PVC bags.