ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

Vimpat 50 mg film-coated tablets

Each film-coated tablet contains 50 mg lacosamide.

Vimpat 100 mg film-coated tablets

Each film-coated tablet contains 100 mg lacosamide.

Vimpat 150 mg film-coated tablets

Each film-coated tablet contains 150 mg lacosamide.

Vimpat 200 mg film-coated tablets

Each film-coated tablet contains 200 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Vimpat 50 mg film-coated tablets
Pinkish, oval film-coated tablets with approximate dimensions of 10.4 mm x 4.9 mm, and debossed with ‘SP’ on one side and ‘50’ on the other side.

Vimpat 100 mg film-coated tablets
Dark yellow, oval film-coated tablets with approximate dimensions of 13.2 mm x 6.1 mm, and debossed with ‘SP’ on one side and ‘100’ on the other side.

Vimpat 150 mg film-coated tablets
Salmon, oval film-coated tablets with approximate dimensions of 15.1 mm x 7.0 mm, and debossed with ‘SP’ on one side and ‘150’ on the other side.

Vimpat 200 mg film-coated tablets
Blue, oval film-coated tablets with approximate dimensions of 16.6 mm x 7.8 mm, and debossed with ‘SP’ on one side and ‘200’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vimpat is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

Vimpat is indicated as adjunctive therapy

- in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Posology

The physician should prescribe the most appropriate formulation and strength according to weight and dose.
The recommended posology for adults, adolescents and children from 2 years of age is summarised in the following table.
Lacosamide must be taken twice a day, approximately 12 hours apart.
If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of lacosamide at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of lacosamide at the regularly scheduled time. Patients should not take a double dose.

Adolescents and children weighing 50 kg or more, and adults		
Starting dose	**Titration (incremental steps)**	**Maximum recommended dose**
Monotherapy: 50 mg twice a day (100 mg/day) or 100 mg twice a day (200 mg/day) **Adjunctive therapy:** 50 mg twice a day (100 mg/day)	50 mg twice a day (100 mg/day) at weekly intervals	**Monotherapy:** up to 300 mg twice a day (600 mg/day) **Adjunctive therapy:** up to 200 mg twice a day (400 mg/day)
Alternate initial dosage* (If applicable)**:** 200 mg single loading dose followed by 100 mg twice a day (200 mg/day)		
*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 serious cardiac arrhythmia and 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.		

<table>
<tr><th colspan="3"><u>Children from 2 years of age and adolescents weighing less than 50 kg*</u></th></tr>
<tr><th>Starting dose</th><th>Titration (incremental steps)</th><th>Maximum recommended dose</th></tr>
<tr><td rowspan="2">Monotherapy and Adjunctive therapy:
1 mg/kg twice a day
(2 mg/kg/day)</td><td rowspan="2">1 mg/kg twice a day
(2 mg/kg/day) at weekly intervals</td><td>Monotherapy:
- up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 40 kg
- up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 40 kg to < 50 kg</td></tr>
<tr><td>Adjunctive therapy:
- up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 20 kg
- up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 20 kg to < 30 kg
- up to 4 mg/kg twice a day (8 mg/kg/day) in patients ≥ 30 kg to < 50 kg</td></tr>
<tr><td colspan="3">* Children less than 50 kg should preferably start the treatment with Vimpat 10 mg/ml syrup.</td></tr>
</table>

<u>Adolescents and children weighing 50 kg or more, and adults</u>

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day (200 mg/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 daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 200 mg twice a day (400 mg/day) and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalised tonic-clonic seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/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 200 mg twice a day (400 mg/day).

Children from 2 years of age and adolescents weighing less than 50 kg

The dose is determined based on body weight. It is therefore recommended to initiate treatment with the syrup and switch to tablets, if desired. When prescribing the syrup, the dose should be expressed in volume (ml) rather than weight (mg).

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.
Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually increased until the optimum response is obtained. The lowest effective dose should be used. In children weighing from 10 kg to less than 40 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 40 to under 50 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended.

Adjunctive therapy (in the treatment of primary generalised tonic-clonic seizures from 4 years of age or in the treatment of partial-onset seizures from 2 years of age)
The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.
Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually adjusted until the optimum response is obtained. The lowest effective dose should be used. Due to an increased clearance compared to adults, in children weighing from 10 kg to less than 20 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 20 to under 30 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended and in children weighing from 30 to under 50 kg, a maximum dose of 4 mg/kg twice a day (8 mg/kg/day) is recommended, although in open-label studies (see sections 4.8 and 5.2), a dose up to 6 mg/kg twice a day (12 mg/kg/day) has been used by a small number of children from this latter group.

Initiation of lacosamide treatment with a loading dose (*initial monotherapy or conversion to monotherapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of primary generalised tonic-clonic seizures)*
In adolescents and children weighing 50 kg or more, and adults, lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice a day (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 serious cardiac arrhythmia and 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
If lacosamide has to be discontinued, it is recommended that the dose is reduced gradually in weekly decrements of 4 mg/kg/day (for patients with a body weight less than 50 kg) or 200 mg/day (for patients with a body weight of 50 kg or more) for patients who have achieved a dose of lacosamide ≥ 6 mg/kg/day or ≥ 300 mg/day, respectively. A slower taper in weekly decrements of 2 mg/kg/day or 100 mg/day can be considered, if medically necessary.
In patients who develop serious cardiac arrhythmia, clinical benefit/risk assessment should be performed and if needed lacosamide should be discontinued.

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 adult and paediatric patients (CL_{CR} > 30 ml/min). In paediatric patients weighing 50 kg or more and in adult 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 paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment (CL_{CR} ≤ 30 ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and 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. In paediatric patients weighing less than 50 kg with severe renal impairment (CL_{CR} ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all 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 paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. In adolescents and adults weighing 50 kg or more, a loading dose of 200 mg may be considered, but further dose titration (> 200 mg daily) should be performed with caution. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric 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

Lacosamide is not recommended for use in children below the age of 4 years in the treatment of primary generalized tonic-clonic seizures and below the age of 2 years in the treatment of partial-onset seizures as there is limited data on safety and efficacy in these age groups, respectively.

Loading dose
Administration of a loading dose has not been studied in children. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg.

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 antiepileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled clinical studies of antiepileptic medicinal products 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 underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products (see section 4.5), as well as in elderly patients.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state.

In the placebo-controlled clinical studies of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if 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).

Potential for new onset or worsening of myoclonic seizures

New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with PGTCS, in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined.

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 (including sodium channel blocking antiepileptic medicinal products) and in patients treated with antiarrhythmics. However, subgroup analysis in clinical studies did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, CYP2B6, and CYP2C9 are not induced and that CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical studies. 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 CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice a day), but C_{max} of midazolam was slightly increased (30 %). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and CYP3A4, lacosamide given 300 mg twice a day).
The CYP2C19 inhibitor omeprazole (40 mg once daily) 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.

Antiepileptic medicinal products

In interaction studies 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. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other antiepileptic medicinal products known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic

exposure of lacosamide by 25 % in adults and 17 % in paediatric patients.

Oral contraceptives

In an interaction study 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 studies 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 medicinal products through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking lacosamide (see Pregnancy).
If a woman decides to become pregnant, the use of lacosamide should be carefully re-evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all antiepileptic medicinal products, it has been shown that in the offspring of treated women 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 antiepileptic 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

Lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. It is recommended that 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 studies in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9 % of patients randomised to lacosamide and 35.2 % of patients randomised 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 clinical studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomised to lacosamide and 1.6 % for patients randomised 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 study 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.

The safety profile of lacosamide reported in a study conducted in patients aged 4 years and older with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures (PGTCS) was consistent with the safety profile reported from the pooled placebo-controlled clinical studies in partial-onset seizures. Additional adverse reactions reported in PGTCS patients were myoclonic epilepsy (2.5 % in the lacosamide-group and 0 % in the placebo-group) and ataxia (3.3 % in the lacosamide-group and 0 % in the placebo-group). The most frequently reported adverse reactions were dizziness and somnolence. The most common adverse reactions resulting in discontinuation of lacosamide therapy were dizziness and suicidal ideation. The discontinuation rate due to adverse reactions was 9.1 % in the lacosamide group and 4.1 % in the placebo group.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical studies 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 Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt[1] Suicidal ideation Hallucination[1]	
Nervous system disorders	Dizziness Headache	Myoclonic seizures[3] Ataxia Balance disorder Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2] Coordination abnormal Dyskinesia	Convulsion
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]	Ventricular tachyarrhythmia[1]
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal[2] Hepatic enzyme increased (> 2x ULN)[1]	

System organ class	Very common	Common	Uncommon	Not known
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.
[(3)] Reported in PGTCS studies.

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 studies 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 study 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 studies 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 study 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 studies; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in placebo-controlled clinical studies with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic medicinal products. 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 medicinal products. 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

The safety profile of lacosamide in placebo-controlled (255 patients from 1 month to less than 4 years of age and 343 patients from 4 years to less than 17 years of age) and in open-label clinical studies (847 patients from 1 month to less than or equal to 18 years of age) in adjunctive therapy in paediatric patients with partial-onset seizures was consistent with the safety profile observed in adults. As data available in paediatric patients younger than 2 years of age is limited, lacosamide is not indicated in this age range.
The additional adverse reactions observed in the paediatric population were pyrexia, nasopharyngitis, pharyngitis, decreased appetite, abnormal behaviour and lethargy. Somnolence was reported more frequently in the paediatric population (≥ 1/10) compared to the adult population (≥ 1/100 to < 1/10).

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, diarrhoea 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 adult 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 adult 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 (generalised 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 generalised 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 (partial-onset seizures)
Adult population

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 generalisation. The patients were randomised 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 1,200 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, randomised study. 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 randomised to be converted to lacosamide monotherapy (either 400 mg/day or 300 mg/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, randomised, placebo-controlled clinical studies with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy studies, 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 studies, involving 1,308 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 antiepileptic medicinal products 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 intravenous lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single intravenous loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the intravenous dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

Paediatric population

Partial-onset seizures have a similar pathophysiology and clinical expression in children from 2 years of age and in adults. The efficacy of lacosamide in children aged 2 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).
The efficacy supported by the extrapolation principle stated above was confirmed by a double-blind, randomised, placebo-controlled clinical study. The study consisted of an 8-week baseline period followed by a 6-week titration period. Eligible patients on a stable dose regimen of 1 to ≤ 3 antiepileptic medicinal products, who still experienced at least 2 partial-onset seizures during the 4 weeks prior to screening with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the baseline period, were randomised to receive either placebo (n=172) or lacosamide (n=171).
Dosing was initiated at a dose of 2 mg/kg/day in subjects weighing less than 50 kg or 100 mg/day in subjects weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 1or 2 mg/kg/day increments in subjects weighing less than 50 kg or 50 or 100 mg/day in subjects weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose range.
Subjects must have achieved the minimum target dose for their body weight category for the final 3 days of the titration period to be eligible for entry into the 10-week maintenance period. Subjects were to remain on stable lacosamide dose throughout the maintenance period or were withdrawn and entered in the blinded taper period.
Statistically significant (p=0.0003) and clinically relevant reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was observed between the lacosamide and the placebo group. The percent reduction over placebo based on analysis of covariance was 31.72 % (95 % CI: 16.342, 44.277).
Overall, the proportion of subjects with at least a 50 % reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was 52.9 % in the lacosamide group compared with 33.3 % in the placebo group.
The quality of life assessed by the Pediatric Quality of Life Inventory indicated that subjects in both lacosamide and placebo groups had a similar and stable health-related quality of life during the entire treatment period.

Clinical efficacy and safety (primary generalized tonic-clonic seizures)

The efficacy of lacosamide as adjunctive therapy in patients 4 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures (PGTCS) was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center clinical study. The study consisted of a 12-week historical baseline period, a 4-week prospective baseline period and a 24-week treatment period (which included a 6-week titration period and an 18-week maintenance period). Eligible patients on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTCS during the 16-week combined baseline period were randomized 1 to 1 to receive lacosamide or placebo (patients in the full analysis set: lacosamide n=118, placebo n=121; of them 8 patients in the ≥ 4 to < 12 years age group and 16 patients in the ≥ 12 to < 18 years range were treated with lacosamide and 9 and 16 patients, respectively with placebo).
Patients were titrated up to the target maintenance period dose of 12 mg/kg/day in patients weighing less than 30 kg, 8 mg/kg/day in patients weighing from 30 to less than 50 kg or 400 mg/day in patients weighing 50 kg or more.

Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Time to second PGTCS		
Median (days)	77.0	-
95 % CI	49.0, 128.0	-
Lacosamide – Placebo		
Hazard Ratio	0.540	
95 % CI	0.377, 0.774	
p-value	< 0.001	
Seizure freedom		
Stratified Kaplan-Meier estimate (%)	17.2	31.3
95 % CI	10.4, 24.0	22.8, 39.9
Lacosamide – Placebo	14.1	
95 % CI	3.2, 25.1	
p-value	0.011	

Note: For the lacosamide group, the median time to second PGTCS could not be estimated by Kaplan-Meier methods because > 50% of patients did not experience a second PGTCS by Day 166.

The findings in the paediatric subgroup were consistent with the results of the overall population for the primary, secondary and other efficacy endpoints.

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 lacosamide 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 study 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 faeces. The elimination half-life of lacosamide 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 studies 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 end-stage renal disease requiring haemodialysis 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 end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage 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).

Paediatric population
The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in six placebo-controlled randomised clinical studies and five open-label studies in 1655 adult and paediatric patients with epilepsy aged 1 month to 17 years. Three of these studies were performed in adults, 7 in pediatric patients, and 1 in a mixed population. The administered lacosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, not to exceed 600 mg/day.
The typical plasma clearance was estimated to be 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 10 kg, 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.74 L/h in adults (70 kg body weight).
Population pharmacokinetic analysis using sparse pharmacokinetic samples from PGTCS study showed a similar exposure in patients with PGTCS and in patients with partial-onset seizures.

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 anesthetised 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 anesthetised 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.
In juvenile rats and dogs, the types of toxicity do not differ qualitatively from those observed in adult animals. In juvenile rats, a reduced body weight was observed at systemic exposure levels similar to the expected clinical exposure. In juvenile dogs, transient and dose-related CNS clinical signs started to be observed at systemic exposure levels below the expected clinical exposure.

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

Vimpat 50 mg film-coated tablets

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

Vimpat 100 mg film-coated tablets

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

Vimpat 150 mg film-coated tablets

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

Vimpat 200 mg film-coated tablets

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

Vimpat 50 mg film-coated tablets

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 tablets in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.
Packs of 60 film-coated tablets in HDPE bottle with a child-resistant closure.

Vimpat 100 mg film-coated tablets

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 tablets in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.
Packs of 60 film-coated tablets in HDPE bottle with a child-resistant closure.

Vimpat 150 mg film-coated tablets

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 tablets in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.
Packs of 60 film-coated tablets in HDPE bottle with a child-resistant closure.

Vimpat 200 mg film-coated tablets

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 tablets in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.
Packs of 60 film-coated tablets in HDPE bottle with a child-resistant closure.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/001
EU/1/08/470/002
EU/1/08/470/003
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EU/1/08/470/030
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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: https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Treatment initiation pack (in adolescents and children weighing 50 kg or more and adults only)
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

Vimpat 50 mg film-coated tablets

Each film-coated tablet contains 50 mg lacosamide.

Vimpat 100 mg film-coated tablets

Each film-coated tablet contains 100 mg lacosamide.

Vimpat 150 mg film-coated tablets

Each film-coated tablet contains 150 mg lacosamide.

Vimpat 200 mg film-coated tablets

Each film-coated tablet contains 200 mg lacosamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Vimpat 50 mg film-coated tablets
Pinkish, oval film-coated tablets with approximate dimensions of 10.4 mm x 4.9 mm, and debossed with ‘SP’ on one side and ‘50’ on the other side.

Vimpat 100 mg film-coated tablets
Dark yellow, oval film-coated tablets with approximate dimensions of 13.2 mm x 6.1 mm, and debossed with ‘SP’ on one side and ‘100’ on the other side.

Vimpat 150 mg film-coated tablets
Salmon, oval film-coated tablets with approximate dimensions of 15.1 mm x 7.0 mm, and debossed with ‘SP’ on one side and ‘150’ on the other side.

Vimpat 200 mg film-coated tablets
Blue, oval film-coated tablets with approximate dimensions of 16.6 mm x 7.8 mm, and debossed with ‘SP’ on one side and ‘200’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vimpat is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

Vimpat is indicated as adjunctive therapy

- in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Posology

The physician should prescribe the most appropriate formulation and strength according to weight and dose.
Lacosamide must be taken twice a day, approximately 12 hours apart.
If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of lacosamide at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of lacosamide at the regularly scheduled time. Patients should not take a double dose.

Adolescents and children weighing 50 kg or more, and adults

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day (200 mg/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 daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 400 mg/day and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalised tonic-clonic seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/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 200 mg twice a day (400 mg/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 (100 mg/day). During the second week, the patient takes Vimpat 100 mg tablets twice a day (200 mg/day). Depending on response and tolerability, Vimpat 150 mg tablets may be taken twice a day (300 mg/day) during the third week and Vimpat 200 mg tablets twice a day (400 mg/day) during the fourth week.

Discontinuation
If lacosamide has to be discontinued, it is recommended that the dose is reduced gradually in weekly decrements of 4 mg/kg/day (for patients with a body weight less than 50 kg) or 200 mg/day (for patients with a body weight of 50 kg or more) for patients who have achieved a dose of lacosamide ≥ 6 mg/kg/day or ≥ 300 mg/day, respectively. A slower taper in weekly decrements of 2 mg/kg/day or 100 mg/day can be considered, if medically necessary.
In patients who develop serious cardiac arrhythmia, clinical benefit/risk assessment should be performed and if needed lacosamide should be discontinued.

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 adult and paediatric patients (CL_{CR} > 30 ml/min). A maximum dose of 250 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with severe renal impairment (CL_{CR} ≤ 30 ml/min) or with end-stage renal disease. In paediatric patients weighing less than 50 kg with severe renal impairment (CL_{CR} ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all 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 paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric 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

Adolescents and children weighing 50 kg or more
Dosage in adolescents and children weighing 50 kg or more is the same as in adults (see above).

Children (from 2 years of age) and adolescents weighing below 50 kg
This presentation is not suitable for this category of patients.

Children less than 2 years of age
The safety and efficacy of lacosamide in children aged below 2 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 antiepileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled clinical studies of antiepileptic medicinal products 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 underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products (see section 4.5), as well as in elderly patients.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state.

In the placebo-controlled clinical studies of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if 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).

Potential for new onset or worsening of myoclonic seizures

New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with PGTCS, in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined.

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 (including sodium channel blocking antiepileptic medicinal products) and in patients treated with antiarrhythmics. However, subgroup analysis in clinical studies did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, CYP2B6, and CYP2C9 are not induced and that CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical studies. 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 CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice a day) but C_{max} of midazolam was slightly increased (30 %). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and CYP3A4, lacosamide given 300 mg twice a day).
The CYP2C19 inhibitor omeprazole (40 mg once daily) 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.

Antiepileptic medicinal products

In interaction studies 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. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other antiepileptic medicinal products known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic

exposure of lacosamide by 25 % in adults and 17 % in paediatric patients.

Oral contraceptives

In an interaction study 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 studies 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 medicinal products through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking lacosamide (see Pregnancy).
If a woman decides to become pregnant, the use of lacosamide should be carefully re-evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all antiepileptic medicinal products, it has been shown that in the offspring of treated women 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 antiepileptic 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

Lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. It is recommended that 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 studies in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9 % of patients randomised to lacosamide and 35.2 % of patients randomised 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 clinical studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomised to lacosamide and 1.6 % for patients randomised 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 study 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.

The safety profile of lacosamide reported in a study conducted in patients aged 4 years and older with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures (PGTCS) was consistent with the safety profile reported from the pooled placebo-controlled clinical studies in partial-onset seizures. Additional adverse reactions reported in PGTCS patients were myoclonic epilepsy (2.5 % in the lacosamide-group and 0 % in the placebo-group) and ataxia (3.3 % in the lacosamide-group and 0 % in the placebo-group). The most frequently reported adverse reactions were dizziness and somnolence. The most common adverse reactions resulting in discontinuation of lacosamide therapy were dizziness and suicidal ideation. The discontinuation rate due to adverse reactions was 9.1 % in the lacosamide group and 4.1 % in the placebo group.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical studies 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 Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt[1] Suicidal ideation Hallucination[1]	
Nervous system disorders	Dizziness Headache	Myoclonic seizures[3] Ataxia Balance disorder Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2] Coordination abnormal Dyskinesia	Convulsion
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]	Ventricular tachyarrhythmia[1]
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal[2] Hepatic enzyme increased (> 2x ULN)[1]	

System organ class	Very common	Common	Uncommon	Not known
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.
[(3)] Reported in PGTCS studies.

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 studies 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 study 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 studies 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 study 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 studies; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in placebo-controlled clinical studies with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic medicinal products. 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 medicinal products. 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

The safety profile of lacosamide in placebo-controlled (255 patients from 1 month to less than 4 years of age and 343 patients from 4 years to less than 17 years of age) and in open-label clinical studies (847 patients from 1 month to less than or equal to 18 years of age) in adjunctive therapy in paediatric patients with partial-onset seizures was consistent with the safety profile observed in adults. As data available in paediatric patients younger than 2 years of age is limited, lacosamide is not indicated in this age range.
The additional adverse reactions observed in the paediatric population were pyrexia, nasopharyngitis, pharyngitis, decreased appetite, abnormal behaviour and lethargy. Somnolence was reported more frequently in the paediatric population (≥ 1/10) compared to the adult population (≥ 1/100 to < 1/10).

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, diarrhoea 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 adult 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 adult 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 (generalised 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 generalised 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 (partial-onset seizures)
Adult population

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 generalisation. The patients were randomised 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 1,200 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, randomised study. 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 randomised to be converted to lacosamide monotherapy (either 400 mg/day or 300 mg/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, randomised, placebo-controlled clinical studies with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy studies, 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 studies, involving 1,308 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 antiepileptic medicinal products 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.

Paediatric population

Partial-onset seizures have a similar pathophysiology and clinical expression in children from 2 years of age and in adults. The efficacy of lacosamide in children aged 2 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).
The efficacy supported by the extrapolation principle stated above was confirmed by a double-blind, randomised, placebo-controlled clinical study. The study consisted of an 8-week baseline period followed by a 6-week titration period. Eligible patients on a stable dose regimen of 1 to ≤ 3 antiepileptic medicinal products, who still experienced at least 2 partial-onset seizures during the 4 weeks prior to screening with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the baseline period, were randomised to receive either placebo (n=172) or lacosamide (n=171).
Dosing was initiated at a dose of 2 mg/kg/day in subjects weighing less than 50 kg or 100 mg/day in subjects weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 1or 2 mg/kg/day increments in subjects weighing less than 50 kg or 50 or 100 mg/day in subjects weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose range.
Subjects must have achieved the minimum target dose for their body weight category for the final 3 days of the titration period to be eligible for entry into the 10-week maintenance period. Subjects were to remain on stable lacosamide dose throughout the maintenance period or were withdrawn and entered in the blinded taper period.
Statistically significant (p=0.0003) and clinically relevant reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was observed between the lacosamide and the placebo group. The percent reduction over placebo based on analysis of covariance was 31.72 % (95 % CI: 16.342, 44.277).
Overall, the proportion of subjects with at least a 50 % reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was 52.9 % in the lacosamide group compared with 33.3 % in the placebo group.
The quality of life assessed by the Pediatric Quality of Life Inventory indicated that subjects in both lacosamide and placebo groups had a similar and stable health-related quality of life during the entire treatment period.

Clinical efficacy and safety (primary generalized tonic-clonic seizures)

The efficacy of lacosamide as adjunctive therapy in patients 4 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures (PGTCS) was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center clinical study. The study consisted of a 12-week historical baseline period, a 4-week prospective baseline period and

a 24-week treatment period (which included a 6-week titration period and an 18-week maintenance period). Eligible patients on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTCS during the 16-week combined baseline period were randomized 1 to 1 to receive lacosamide or placebo (patients in the full analysis set: lacosamide n=118, placebo n=121; of them 8 patients in the ≥ 4 to < 12 years age group and 16 patients in the ≥ 12 to < 18 years range were treated with lacosamide and 9 and 16 patients, respectively with placebo).
Patients were titrated up to the target maintenance period dose of 12 mg/kg/day in patients weighing less than 30 kg, 8 mg/kg/day in patients weighing from 30 to less than 50 kg or 400 mg/day in patients weighing 50 kg or more.

Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Time to second PGTCS		
Median (days)	77.0	-
95 % CI	49.0, 128.0	-
Lacosamide – Placebo		
Hazard Ratio	0.540	
95 % CI	0.377, 0.774	
p-value	< 0.001	
Seizure freedom		
Stratified Kaplan-Meier estimate (%)	17.2	31.3
95 % CI	10.4, 24.0	22.8, 39.9
Lacosamide – Placebo	14.1	
95 % CI	3.2, 25.1	
p-value	0.011	

Note: For the lacosamide group, the median time to second PGTCS could not be estimated by Kaplan-Meier methods because > 50% of patients did not experience a second PGTCS by Day 166.

The findings in the paediatric subgroup were consistent with the results of the overall population for the primary, secondary and other efficacy endpoints.

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 lacosamide 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 study 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 faeces. The elimination half-life of lacosamide 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 studies 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 end-stage renal disease requiring haemodialysis 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 end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage 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).

Paediatric population
The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in six placebo-controlled randomised clinical studies and five open-label studies in 1655 adult and paediatric patients with epilepsy aged 1 month to 17 years. Three of these studies were performed in adults, 7 in pediatric patients, and 1 in a mixed population. The administered lacosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, not to exceed 600 mg/day.
The typical plasma clearance was estimated to be 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 10 kg, 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.74 L/h in adults (70 kg body weight).
Population pharmacokinetic analysis using sparse pharmacokinetic samples from PGTCS study showed a similar exposure in patients with PGTCS and in patients with partial-onset seizures.

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 anesthetised 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 anesthetised 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.
In juvenile rats and dogs, the types of toxicity do not differ qualitatively from those observed in adult animals. In juvenile rats, a reduced body weight was observed at systemic exposure levels similar to the expected clinical exposure. In juvenile dogs, transient and dose-related CNS clinical signs started to be observed at systemic exposure levels below the expected clinical exposure.

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)

Vimpat 50 mg film-coated tablets: red iron oxide (E172), black iron oxide (E172), indigo carmine aluminium lake (E132)
Vimpat 100 mg film-coated tablets: yellow iron oxide (E172)
Vimpat 150 mg film-coated tablets: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172)
Vimpat 200 mg film-coated 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 Vimpat film-coated tablets of 50 mg, 100 mg, 150 mg and 200 mg.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
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: https://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.

Excipients with known effect:
Each ml of Vimpat syrup contains 187 mg sorbitol (E420), 2.60 mg sodium methyl parahydroxybenzoate (E219), 2.14 mg propylene glycol (E1520), 1.42 mg sodium and 0.032 mg aspartame (E951).

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 in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

Vimpat is indicated as adjunctive therapy

- in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Posology

The physician should prescribe the most appropriate formulation and strength according to weight and dose.
The recommended posology for adults, adolescents and children from 2 years of age is summarised in the following table.
Lacosamide must be taken twice a day, approximately 12 hours apart.
If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of lacosamide at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of lacosamide at the regularly scheduled time. Patients should not take a double dose.

Adolescents and children weighing 50 kg or more, and adults		
Starting dose	**Titration (incremental steps)**	**Maximum recommended dose**
Monotherapy: 50 mg twice a day (100 mg/day) or 100 mg twice a day (200 mg/day) **Adjunctive therapy:** 50 mg twice a day (100 mg/day)	50 mg twice a day (100 mg/day) at weekly intervals	**Monotherapy:** up to 300 mg twice a day (600 mg/day) **Adjunctive therapy:** up to 200 mg twice a day (400 mg/day)
Alternate initial dosage* (If applicable)**:** 200 mg single loading dose followed by 100 mg twice a day (200 mg/day)		
* 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 serious cardiac arrhythmia and 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.		

Children from 2 years of age and adolescents weighing less than 50 kg		
Starting dose	**Titration (incremental steps)**	**Maximum recommended dose**
Monotherapy and Adjunctive therapy: 1 mg/kg twice a day (2 mg/kg/day)	1 mg/kg twice a day (2 mg/kg/day) at weekly intervals	**Monotherapy:** - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 40 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 40 kg to < 50 kg
		Adjunctive therapy: - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 20 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 20 kg to < 30 kg - up to 4 mg/kg twice a day (8 mg/kg/day) in patients ≥ 30 kg to < 50 kg

Adolescents and children weighing 50 kg or more, and adults

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day (200 mg/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 daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 200 mg twice a day (400 mg/day) and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalised tonic-clonic seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/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 200 mg twice a day (400 mg/day) .

Children from 2 years of age and adolescents weighing less than 50 kg

The dose is determined based on body weight. It is therefore recommended to initiate treatment with the syrup and switch to tablets, if desired. When prescribing the syrup, the dose should be expressed in volume (ml) rather than weight (mg).

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.
Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually increased until the optimum response is obtained. The lowest effective dose should be used. In children weighing from 10 kg to less than 40 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 40 to under 50 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended.

The tables below provide examples of volumes of syrup per intake depending on prescribed dose and body weight. The precise volume of syrup is to be calculated according to the exact body weight of the child. The calculated volume should be rounded to the nearest measuring device graduated increment. If the calculated volume is equidistant between two graduated increments, the larger graduated increment should be used (see Method of administration).

Monotherapy doses in the treatment of partial-onset seizures **to be taken twice a day** for children from 2 years of age **weighing from 10 kg to less than 40 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg)	0.6 ml/kg (6 mg/kg) Maximum recommended dose
Recommended device:	10 ml syringe for volume between 1 ml and 20 ml *30 ml measuring cup for volume more than 20 ml					
Weight	Volume administered					
10 kg	1 ml (10 mg)	2 ml (20 mg)	3 ml (30 mg)	4 ml (40 mg)	5 ml (50 mg)	6 ml (60 mg)
15 kg	1.5 ml (15 mg)	3 ml (30 mg)	4.5 ml (45 mg)	6 ml (60 mg)	7.5 ml (75 mg)	9 ml (90 mg)
20 kg	2 ml (20 mg)	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)	10 ml (100 mg)	12 ml (120 mg)
25 kg	2.5 ml (25 mg)	5 ml (50 mg)	7.5 ml (75 mg)	10 ml (100 mg)	12.5 ml (125 mg)	15 ml (150 mg)
30 kg	3 ml (30 mg)	6 ml (60 mg)	9 ml (90 mg)	12 ml (120 mg)	15 ml (150 mg)	18 ml (180 mg)
35 kg	3.5 ml (35 mg)	7 ml (70 mg)	10.5 ml (105 mg)	14 ml (140 mg)	17.5 ml (175 mg)	21 ml* (210 mg)
For volume between 1 ml and 20 ml, the patient should be instructed to use the 10 ml oral syringe. * For volume above 20 ml, the patient should be instructed to use the 30 ml measuring cup.						

Monotherapy doses in the treatment of partial-onset seizures **to be taken twice a day** for children and adolescents **weighing from 40 kg to less than 50 kg**[(1)]

Week	Week 1	Week 2	Week 3	Week 4	Week 5
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg) Maximum recommended dose
Recommended device:	10 ml syringe for volume between 1 ml and 20 ml *30 ml measuring cup for volume more than 20 ml				
Weight	Volume administered				
40 kg	4 ml (40 mg)	8 ml (80 mg)	12 ml (120 mg)	16 ml (160 mg)	20 ml (200 mg)
45 kg	4.5 ml (45 mg)	9 ml (90 mg)	13.5 ml (135 mg)	18 ml (180 mg)	22.5 ml* (225 mg)
[(1)] Dosage in adolescents 50 kg or more is the same as in adults.					
For volume between 1 ml and 20 ml, the patient should be instructed to use the 10 ml oral syringe. * For volume above 20 ml, the patient should be instructed to use the 30 ml measuring cup.					

Adjunctive therapy (in the treatment of primary generalised tonic-clonic seizures from 4 years of age or in the treatment of partial-onset seizures from 2 years of age)
The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.
Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually adjusted until the optimum response is obtained. The lowest effective dose should be used. Due to an increased clearance compared to adults, in children weighing from 10 kg to less than 20 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 20 to under 30 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended and in children weighing from 30 to under 50 kg, a maximum dose of 4 mg/kg twice a day (8 mg/kg/day) is recommended, although in open-label studies (see sections 4.8 and 5.2), a dose up to 6 mg/kg twice a day (12 mg/kg/day) has been used by a small number of children from this latter group.

The tables below provide examples of volumes of syrup per intake depending on prescribed dose and body weight. The precise volume of syrup is to be calculated according to the exact body weight of the child. The calculated volume should be rounded to the nearest measuring device graduated increment. If the calculated volume is equidistant between two graduated increments, the larger graduated increment should be used.

Adjunctive therapy doses **to be taken twice a day** for children from 2 years **weighing from 10 kg to less than 20 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg)	0.6 ml/kg (6 mg/kg) Maximum recommended dose
Recommended device:	10 ml syringe for volume between 1 ml and 20 ml					
Weight	Volume administered					
10 kg	1 ml (10 mg)	2 ml (20 mg)	3 ml (30 mg)	4 ml (40 mg)	5 ml (50 mg)	6 ml (60 mg)
12 kg	1.2 ml (12 mg)	2.4 ml (24 mg)	3.6 ml (36 mg)	4.8 ml (48 mg)	6 ml (60 mg)	7.2 ml (72 mg)
14 kg	1.4 ml (14 mg)	2.8 ml (28 mg)	4.2 ml (42 mg)	5.6 ml (56 mg)	7 ml (70 mg)	8.4 ml (84 mg)
15 kg	1.5 ml (15 mg)	3 ml (30 mg)	4.5 ml (45 mg)	6 ml (60 mg)	7.5 ml (75 mg)	9 ml (90 mg)
16 kg	1.6 ml (16 mg)	3.2 ml (32 mg)	4.8 ml (48 mg)	6.4 ml (64 mg)	8 ml (80 mg)	9.6 ml (96 mg)
18 kg	1.8 ml (18 mg)	3.6 ml (36 mg)	5.4 ml (54 mg)	7.2 ml (72 mg)	9 ml (90 mg)	10.8 ml (108 mg)

Adjunctive therapy doses **to be taken twice a day** for children and adolescents **weighing from 20 kg to less than 30 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg) Maximum recommended dose
Recommended device:	10 ml syringe for volume between 1 ml and 20 ml				
Weight	Volume administered				
20 kg	2 ml (20 mg)	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)	10 ml (100 mg)
22 kg	2.2 ml (22 mg)	4.4 ml (44mg)	6.6 ml (66 mg)	8.8 ml (88 mg)	11 ml (110 mg)
24 kg	2.4 ml (24 mg)	4.8 ml (48 mg)	7.2 ml (72 mg)	9.6 ml (96 mg)	12 ml (120 mg)
25 kg	2.5 ml (25 mg)	5 ml (50 mg)	7.5 ml (75 mg)	10 ml (100 mg)	12.5 ml (125 mg)
26 kg	2.6 ml (26 mg)	5.2 ml (52 mg)	7.8 ml (78 mg)	10.4 ml (104 mg)	13 ml (130 mg)
28 kg	2.8 ml (28 mg)	5.6 ml (56 mg)	8.4 ml (84 mg)	11.2 ml (112 mg)	14 ml (140 mg)

Adjunctive therapy doses **to be taken twice a day** for children and adolescents **weighing from 30 kg to less than 50 kg**

Week	Week 1	Week 2	Week 3	Week 4
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg) Maximum recommended dose
Recommended device:	10 ml syringe for volume between 1 ml and 20 ml			
Weight	Volume administered			
30 kg	3 ml (30 mg)	6 ml (60 mg)	9 ml (90 mg)	12 ml (120 mg)
35 kg	3.5 ml (35 mg)	7 ml (70 mg)	10.5 ml (105 mg)	14 ml (140 mg)
40 kg	4 ml (40 mg)	8 ml (80 mg)	12 ml (120 mg)	16 ml (160 mg)
45 kg	4.5 ml (45 mg)	9 ml (90 mg)	13.5 ml (135 mg)	18 ml (180 mg)

Initiation of lacosamide treatment with a loading dose (initial monotherapy or conversion to monotherapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of primary generalised tonic-clonic seizures)

In adolescents and children weighing 50 kg or more, and adults, lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice a day (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 serious cardiac

arrhythmia and 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
If lacosamide has to be discontinued, it is recommended that the dose is reduced gradually in weekly decrements of 4 mg/kg/day (for patients with a body weight less than 50 kg) or 200 mg/day (for patients with a body weight of 50 kg or more) for patients who have achieved a dose of lacosamide ≥ 6 mg/kg/day or ≥ 300 mg/day, respectively. A slower taper in weekly decrements of 2 mg/kg/day or 100 mg/day can be considered, if medically necessary.
In patients who develop serious cardiac arrhythmia, clinical benefit/risk assessment should be performed and if needed lacosamide should be discontinued.

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 adult and paediatric patients (CL_{CR} > 30 ml/min). In paediatric patients weighing 50 kg or more and in adult 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 paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment (CL_{CR} ≤ 30 ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and 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. In paediatric patients weighing less than 50 kg with severe renal impairment (CL_{CR} ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all 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 paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. In adolescents and adults weighing 50 kg or more, a loading dose of 200 mg may be considered, but further dose titration (> 200 mg daily) should be performed with caution. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric 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

Lacosamide is not recommended for use in children below the age of 4 years in the treatment of primary generalized tonic-clonic seizures and below the age of 2 years in the treatment of partial-onset seizures as there is limited data on safety and efficacy in these age groups.

Loading dose
Administration of a loading dose has not been studied in children. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg.

Method of administration

Lacosamide syrup must be taken orally.

The bottle containing Vimpat syrup should be shaken well before use. Lacosamide may be taken with or without food.
Lacosamide syrup is provided with:

- a 30 ml measuring cup. One full measuring cup (30 ml) corresponds to 300 mg of lacosamide. The minimum volume is 5 ml which corresponds to 50 mg of lacosamide. As from the 5 ml graduation mark, each increment corresponds to 5 ml which is 50 mg of lacosamide;
- a 10 ml oral syringe (black graduation marks) with an adaptor. One full oral syringe (10 ml) corresponds to 100 mg of lacosamide. The minimum extractable volume is 1 ml which is 10 mg of lacosamide. As from the 1 ml graduation mark, each increment corresponds to 0.25 ml which is 2.5 mg of Lacosamide.

The physician should instruct the patient on the appropriate measuring device to use.

If the required dose is between 10 mg (1 ml) and 100 mg (10 ml), the 10 ml oral syringe should be used.
If the required dose is between 100 mg (10 ml) and 200 mg (20 ml), the 10 ml oral syringe should be used two times.
If the required dose is more than 200 mg (20 ml), the 30 ml measuring cup should be used.
The dose should be rounded to the nearest graduated increment.

Instructions for use are provided in the package leaflet.

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 antiepileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled clinical studies of antiepileptic medicinal products 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 underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or

patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products (see section 4.5), as well as in elderly patients.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state.

In the placebo-controlled clinical studies of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if 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).

Potential for new onset or worsening of myoclonic seizures

New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with PGTCS, in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined.

Excipients

Excipients which may cause intolerance
Vimpat syrup contains sodium methyl parahydroxybenzoate (E219), which may cause allergic reactions (possibly delayed).
Vimpat syrup contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
Vimpat syrup contains aspartame (E951), a source of phenylalanine, which may be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.
Vimpat syrup contains propylene glycol (E1520).

Sodium content
Vimpat syrup contains 1.42 mg sodium per ml, equivalent to 0.07 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Potassium content
This medicine contains potassium, less than 1 mmol (39 mg) per 60 ml, i.e. essentially 'potassium-free'.

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 (including sodium channel blocking antiepileptic medicinal products) and in patients treated with antiarrhythmics. However, subgroup analysis in clinical studies did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, CYP2B6, and CYP2C9 are not induced and that CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical studies. 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 CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice a day) but C_{max} of midazolam was slightly increased (30 %). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and CYP3A4, lacosamide given 300 mg twice a day).
The CYP2C19 inhibitor omeprazole (40 mg once daily) 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.

Antiepileptic medicinal products

In interaction studies 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. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other antiepileptic medicinal products known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25 % in adults and 17 % in paediatric patients.

Oral contraceptives

In an interaction study 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 studies 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 medicinal products through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking lacosamide (see Pregnancy).
If a woman decides to become pregnant, the use of lacosamide should be carefully re-evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all antiepileptic medicinal products, it has been shown that in the offspring of treated women 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 antiepileptic 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

Lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. It is recommended that 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 studies in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9 % of patients randomised to lacosamide and 35.2 % of patients randomised 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 clinical studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomised to lacosamide and 1.6 % for patients randomised 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 study 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.

The safety profile of lacosamide reported in a study conducted in patients aged 4 years and older with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures (PGTCS) was consistent with the safety profile reported from the pooled placebo-controlled clinical studies in partial-onset seizures. Additional adverse reactions reported in PGTCS patients were myoclonic epilepsy (2.5 % in the lacosamide-group and 0 % in the placebo-group) and ataxia (3.3 % in the lacosamide-group and 0 % in the placebo-group). The most frequently reported adverse reactions were dizziness and somnolence. The most common adverse reactions resulting in discontinuation of lacosamide therapy were dizziness and suicidal ideation. The discontinuation rate due to adverse reactions was 9.1 % in the lacosamide group and 4.1 % in the placebo group.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical studies 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)]

System organ class	Very common	Common	Uncommon	Not known
Psychiatric disorders		Depression Confusional state Insomnia[1]	Aggression Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt [1] Suicidal ideation Hallucination [1]	
Nervous system disorders	Dizziness Headache	Myoclonic seizures[3] Ataxia Balance disorder Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2] Coordination abnormal Dyskinesia	Convulsion
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]	Ventricular tachyarrhythmia [1]
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		

System organ class	Very common	Common	Uncommon	Not known
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.
(3) Reported in PGTCS studies.

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 studies 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 study 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 studies 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 study 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 studies; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in placebo-controlled clinical studies with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic medicinal products. 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 medicinal products. 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

The safety profile of lacosamide in placebo-controlled (255 patients from 1 month to less than 4 years of age and 343 patients from 4 years to less than 17 years of age) and in open-label clinical studies (847 patients from 1 month to less than or equal to 18 years of age) in adjunctive therapy in paediatric patients with partial-onset seizures was consistent with the safety profile observed in adults. As data available in paediatric patients younger than 2 years of age is limited, lacosamide is not indicated in this age range.

The additional adverse reactions observed in the paediatric population were pyrexia, nasopharyngitis, pharyngitis, decreased appetite, abnormal behaviour and lethargy. Somnolence was reported more frequently in the paediatric population (≥ 1/10) compared to the adult population (≥ 1/100 to < 1/10).

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, diarrhoea 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 adult 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 adult 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 (generalised 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 generalised 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 (partial-onset seizures)
Adult population

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 generalisation. The patients were randomised 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 1,200 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, randomised study. 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 randomised to be converted to lacosamide monotherapy (either 400 mg/day or 300 mg/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, randomised, placebo-controlled clinical studies with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy studies, 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 studies, involving 1,308 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 antiepileptic medicinal products 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 intravenous lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single intravenous loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the intravenous dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

Paediatric population

Partial-onset seizures have a similar pathophysiology and clinical expression in children from 2 years of age and in adults. The efficacy of lacosamide in children aged 2 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).
The efficacy supported by the extrapolation principle stated above was confirmed by a double-blind, randomised, placebo-controlled clinical study. The study consisted of an 8-week baseline period followed by a 6-week titration period. Eligible patients on a stable dose regimen of 1 to ≤ 3 antiepileptic medicinal products, who still experienced at least 2 partial-onset seizures during the 4 weeks prior to screening with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the baseline period, were randomised to receive either placebo (n=172) or lacosamide (n=171).
Dosing was initiated at a dose of 2 mg/kg/day in subjects weighing less than 50 kg or 100 mg/day in subjects weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 1or 2 mg/kg/day increments in subjects weighing less than 50 kg or 50 or 100 mg/day in subjects weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose range.
Subjects must have achieved the minimum target dose for their body weight category for the final 3 days of the titration period to be eligible for entry into the 10-week maintenance period. Subjects were to remain on stable lacosamide dose throughout the maintenance period or were withdrawn and entered in the blinded taper period.
Statistically significant (p=0.0003) and clinically relevant reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was observed between the lacosamide and the placebo group. The percent reduction over placebo based on analysis of covariance was 31.72 % (95 % CI: 16.342, 44.277).
Overall, the proportion of subjects with at least a 50 % reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was 52.9 % in the lacosamide group compared with 33.3 % in the placebo group.
The quality of life assessed by the Pediatric Quality of Life Inventory indicated that subjects in both lacosamide and placebo groups had a similar and stable health-related quality of life during the entire treatment period.

Clinical efficacy and safety (primary generalized tonic-clonic seizures)

The efficacy of lacosamide as adjunctive therapy in patients 4 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures (PGTCS) was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center clinical study. The study consisted of a 12-week historical baseline period, a 4-week prospective baseline period and a 24-week treatment period (which included a 6-week titration period and an 18-week maintenance period). Eligible patients on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTCS during the 16-week combined baseline period were randomized 1 to 1 to receive lacosamide or placebo (patients in the full analysis set: lacosamide n=118, placebo n=121; of them 8 patients in the ≥ 4 to < 12 years age group and 16 patients in the ≥ 12 to < 18 years range were treated with lacosamide and 9 and 16 patients, respectively with placebo).

Patients were titrated up to the target maintenance period dose of 12 mg/kg/day in patients weighing less than 30 kg, 8 mg/kg/day in patients weighing from 30 to less than 50 kg or 400 mg/day in patients weighing 50 kg or more.

Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Time to second PGTCS		
Median (days)	77.0	-
95 % CI	49.0, 128.0	-
Lacosamide – Placebo		
Hazard Ratio	0.540	
95 % CI	0.377, 0.774	
p-value	< 0.001	
Seizure freedom		
Stratified Kaplan-Meier estimate (%)	17.2	31.3
95 % CI	10.4, 24.0	22.8, 39.9
Lacosamide – Placebo	14.1	
95 % CI	3.2, 25.1	
p-value	0.011	

Note: For the lacosamide group, the median time to second PGTCS could not be estimated by Kaplan-Meier methods because > 50% of patients did not experience a second PGTCS by Day 166.

The findings in the paediatric subgroup were consistent with the results of the overall population for the primary, secondary and other efficacy endpoints.

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 lacosamide 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 study 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 faeces. The elimination half-life of lacosamide 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 studies 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 end-stage renal disease requiring haemodialysis 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 end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage 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).

Paediatric population
The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic

analysis using sparse plasma concentration data obtained in six placebo-controlled randomised clinical studies and five open-label studies in 1655 adult and paediatric patients with epilepsy aged 1 month to 17 years. Three of these studies were performed in adults, 7 in pediatric patients, and 1 in a mixed population. The administered lacosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, not to exceed 600 mg/day.
The typical plasma clearance was estimated to be 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 10 kg, 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.74 L/h in adults (70 kg body weight).
Population pharmacokinetic analysis using sparse pharmacokinetic samples from PGTCS study showed a similar exposure in patients with PGTCS and in patients with partial-onset seizures.

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 anesthetised 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 anesthetised 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.
In juvenile rats and dogs, the types of toxicity do not differ qualitatively from those observed in adult animals. In juvenile rats, a reduced body weight was observed at systemic exposure levels similar to the expected clinical exposure. In juvenile dogs, transient and dose-related CNS clinical signs started to be observed at systemic exposure levels below the expected clinical exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Carmellose sodium
Sorbitol liquid (crystallizing) (E420)
Polyethylene glycol 4000
Sodium chloride
Citric acid, anhydrous
Acesulfame potassium (E950)
Sodium methyl parahydroxybenzoate (E219)
Strawberry flavour (contains propylene glycol (E1520), maltol)
Masking flavour (contains propylene glycol (E1520), aspartame (E951), acesulfame potassium (E950), maltol, deionised water)

purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
After first opening: 6 months.

6.4 Special precautions for storage

Do not refrigerate.

6.5 Nature and contents of container

A 200 ml amber glass bottle with white polypropylene screw cap, a 30 ml polypropylene measuring cup and a 10 ml oral polyethylene / polypropylene syringe (black graduation marks) with a polyethylene adaptor.
One full 30 ml measuring cup corresponds to 300 mg of lacosamide. The minimum volume is 5 ml which corresponds to 50 mg of lacosamide. As from the 5 ml graduation mark, each graduation mark corresponds to 5 ml which is 50 mg of lacosamide (for example 2 graduation marks correspond to 100 mg).
One full 10 ml oral syringe corresponds to 100 mg of lacosamide. The minimum extractable volume is 1 ml which corresponds to10 mg of lacosamide. As from the 1 ml graduation mark, each graduation mark corresponds to 0.25 ml which is 2.5 mg of lacosamide.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/018

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: https://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 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 in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

Vimpat is indicated as adjunctive therapy

- in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

Posology

The physician should prescribe the most appropriate formulation and strength according to weight and dose.
Lacosamide therapy can be initiated with either oral administration (either tablets or syrup) or intravenous administration (solution for infusion). Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with intravenous lacosamide is at the physician's discretion; there is experience from clinical studies with twice daily infusions of lacosamide for up to 5 days in adjunctive therapy. 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. 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 (approximately 12 hours apart).

The recommended posology for adults, adolescents and children from 2 years of age is summarised in the following table.

Adolescents and children weighing 50 kg or more, and adults		
Starting dose	**Titration (incremental steps)**	**Maximum recommended dose**
Monotherapy: 50 mg twice a day (100 mg/day) or 100 mg twice a day (200 mg/day) **Adjunctive therapy:** 50 mg twice a day (100 mg/day)	50 mg twice a day (100 mg/day) at weekly intervals	**Monotherapy:** up to 300 mg twice a day (600 mg/day) **Adjunctive therapy:** up to 200 mg twice a day (400 mg/day)
Alternate initial dosage* (If applicable)**:** 200 mg single loading dose followed by 100 mg twice a day (200 mg/day)		
* 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 serious cardiac arrhythmia and 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.		

Children from 2 years of age and adolescents weighing less than 50 kg		
Starting dose	**Titration (incremental steps)**	**Maximum recommended dose**
Monotherapy and Adjunctive therapy: 1 mg/kg twice a day (2 mg/kg/day)	1 mg/kg twice a day (2 mg/kg/day) at weekly intervals	**Monotherapy:** - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 40 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 40 kg to < 50 kg
		Adjunctive therapy: - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 20 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 20 kg to < 30 kg - up to 4 mg/kg twice a day (8 mg/kg/day) in patients ≥ 30 kg to < 50 kg

Adolescents and children weighing 50 kg or more, and adults

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.
Lacosamide can also be initiated at the dose of 100 mg twice a day (200 mg/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 daily dose of 300 mg twice a day (600 mg/day).
In patients having reached a dose greater than 200 mg twice a day (400 mg/day) and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalised tonic-clonic seizures)
The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/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 200 mg twice a day (400 mg/day).

Children from 2 years of age and adolescents weighing less than 50 kg

The dose is determined based on body weight.

Monotherapy (in the treatment of partial-onset seizures)
The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.
Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually increased until the optimum response is obtained. The lowest effective dose should be used. In children weighing from 10 kg to less than 40 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 40 to under 50 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended.

The tables below provide examples of volumes of solution for infusion per administration depending on prescribed dose and body weight. The precise volume of solution for infusion is to be calculated according to the exact body weight of the child.

Monotherapy doses in the treatment of partial-onset seizures **to be taken twice a day** for children from 2 years of age **weighing from 10 kg to less than 40 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg)	0.6 ml/kg (6 mg/kg) Maximum recommended dose
Weight	Volume administered					
10 kg	1 ml (10 mg)	2 ml (20 mg)	3 ml (30 mg)	4 ml (40 mg)	5 ml (50 mg)	6 ml (60 mg)
15 kg	1.5 ml (15 mg)	3 ml (30 mg)	4.5 ml (45 mg)	6 ml (60 mg)	7.5 ml (75 mg)	9 ml (90 mg)
20 kg	2 ml (20 mg)	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)	10 ml (100 mg)	12 ml (120 mg)
25 kg	2.5 ml (25 mg)	5 ml (50 mg)	7.5 ml (75 mg)	10 ml (100 mg)	12.5 ml (125 mg)	15 ml (150 mg)
30 kg	3 ml (30 mg)	6 ml (60 mg)	9 ml (90 mg)	12 ml (120 mg)	15 ml (150 mg)	18 ml (180 mg)
35 kg	3.5 ml (35 mg)	7 ml (70 mg)	10.5 ml (105 mg)	14 ml (140 mg)	17.5 ml (175 mg)	21 ml (210 mg)

Monotherapy doses in the treatment of partial-onset seizures **to be taken twice a day** for children and adolescents **weighing from 40 kg to less than 50 kg**[(1)]

Week	Week 1	Week 2	Week 3	Week 4	Week 5
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg) Maximum recommended dose
Weight	Volume administered				
40 kg	4 ml (40 mg)	8 ml (80 mg)	12 ml (120 mg)	16 ml (160 mg)	20 ml (200 mg)
45 kg	4.5 ml (45 mg)	9 ml (90 mg)	13.5 ml (135 mg)	18 ml (180 mg)	22.5 ml (225 mg)

[(1)] Dosage in adolescents 50 kg or more is the same as in adults.

Adjunctive therapy (in the treatment of primary generalised tonic-clonic seizures from 4 years of age or in the treatment of partial-onset seizures from 2 years of age)

The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.

Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually adjusted until the optimum response is obtained. The lowest effective dose should be used. Due to an increased clearance compared to adults, in children weighing from 10 kg to less than 20 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 20 to under 30 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended and in children weighing from 30 to under 50 kg, a maximum dose of 4 mg/kg twice a day (8 mg/kg/day) is recommended, although in open-label studies (see sections 4.8 and 5.2), a dose up to 6 mg/kg twice a day (12 mg/kg/day) has been used by a small number of children from this latter group.

The tables below provide examples of volumes of solution for infusion per administration depending on prescribed dose and body weight. The precise volume of solution for infusion is to be calculated according to the exact body weight of the child.

Adjunctive therapy doses **to be taken twice a day** for children from 2 years of age **weighing from 10 kg to less than 20 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg)	0.6 ml/kg (6 mg/kg) Maximum recommended dose
Weight	Volume administered					
10 kg	1 ml (10 mg)	2 ml (20 mg)	3 ml (30 mg)	4 ml (40 mg)	5 ml (50 mg)	6 ml (60 mg)
15 kg	1.5 ml (15 mg)	3 ml (30 mg)	4.5 ml (45 mg)	6 ml (60 mg)	7.5 ml (75 mg)	9 ml (90 mg)

Adjunctive therapy doses **to be taken twice a day** for children and adolescents **weighing from 20 kg to less than 30 kg**

Week	Week 1	Week 2	Week 3	Week 4	Week 5
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg)	0.5 ml/kg (5 mg/kg) Maximum recommended dose
Weight	Volume administered				
20 kg	2 ml (20 mg)	4 ml (40 mg)	6 ml (60 mg)	8 ml (80 mg)	10 ml (100 mg)
25 kg	2.5 ml (25 mg)	5 ml (50 mg)	7.5 ml (75 mg)	10 ml (100 mg)	12.5 ml (125 mg)

Adjunctive therapy doses **to be taken twice a day** for children and adolescents **weighing from 30 kg to less than 50 kg**

Week	Week 1	Week 2	Week 3	Week 4
Prescribed dose	0.1 ml/kg (1 mg/kg) Starting dose	0.2 ml/kg (2 mg/kg)	0.3 ml/kg (3 mg/kg)	0.4 ml/kg (4 mg/kg) Maximum recommended dose
Weight	Volume administered			
30 kg	3 ml (30 mg)	6 ml (60 mg)	9 ml (90 mg)	12 ml (120 mg)
35 kg	3.5 ml (35 mg)	7 ml (70 mg)	10.5 ml (105 mg)	14 ml (140 mg)
40 kg	4 ml (40 mg)	8 ml (80 mg)	12 ml (120 mg)	16 ml (160 mg)
45 kg	4.5 ml (45 mg)	9 ml (90 mg)	13.5 ml (135 mg)	18 ml (180 mg)

Initiation of lacosamide treatment with a loading dose (*initial monotherapy or conversion to monotherapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of primary generalised tonic-clonic seizures)*

In adolescents and children weighing 50 kg or more, and adults, lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice a day (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 serious cardiac arrhythmia and 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
If lacosamide has to be discontinued, it is recommended that the dose is reduced gradually in weekly decrements of 4 mg/kg/day (for patients with a body weight less than 50 kg) or 200 mg/day (for patients with a body weight of 50 kg or more) for patients who have achieved a dose of lacosamide ≥ 6 mg/kg/day or ≥ 300 mg/day, respectively. A slower taper in weekly decrements of 2 mg/kg/day or 100 mg/day can be considered, if medically necessary.
In patients who develop serious cardiac arrhythmia, clinical benefit/risk assessment should be performed and if needed lacosamide should be discontinued.

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 adult and paediatric patients (CL_{CR} > 30 ml/min). In paediatric patients weighing 50 kg or more and in adult 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 paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment (CL_{CR} ≤ 30 ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and 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. In paediatric patients weighing less than 50 kg with severe renal impairment (CL_{CR} ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all 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 paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. In adolescents and adults weighing 50 kg or more, a loading dose of 200 mg may be considered, but further dose titration (> 200 mg daily) should be performed with caution. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric 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

Lacosamide is not recommended for use in children below the age of 4 years in the treatment of primary generalized tonic-clonic seizures and below the age of 2 years in the treatment of partial-onset seizures as there is limited data on safety and efficacy in these age groups.

Loading dose
Administration of a loading dose has not been studied in children. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg.

Method of administration

The solution for infusion is infused over a period of 15 to 60 minutes twice a day. 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 antiepileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled clinical studies of antiepileptic medicinal products 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 underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products (see section 4.5), as well as in elderly patients.
In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400 mg/day and after lacosamide is titrated to steady-state.

In the placebo-controlled clinical studies of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if 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).

Excipients

This medicinal product contains 59.8 mg sodium per vial, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Potential for new onset or worsening of myoclonic seizures

New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with PGTCS, in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

The safety and efficacy of lacosamide in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined.

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 (including sodium channel blocking antiepileptic medicinal products) and in patients treated with antiarrhythmics. However, subgroup analysis in clinical studies did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* studies indicate that the enzymes CYP1A2, CYP2B6, and CYP2C9 are not induced and that CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2E1 are not inhibited by lacosamide at plasma concentrations observed in clinical studies. 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 CYP3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice a day) but C_{max} of midazolam was slightly increased (30 %). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and CYP3A4, lacosamide given

300 mg twice a day).
The CYP2C19 inhibitor omeprazole (40 mg once daily) 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.

Antiepileptic medicinal products

In interaction studies 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. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other antiepileptic medicinal products known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of lacosamide by 25 % in adults and 17 % in paediatric patients.

Oral contraceptives

In an interaction study 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 studies 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 medicinal products through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Physicians should discuss family planning and contraception with women of childbearing potential taking lacosamide (see Pregnancy).
If a woman decides to become pregnant, the use of lacosamide should be carefully re-evaluated.

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general
For all antiepileptic medicinal products, it has been shown that in the offspring of treated women 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 antiepileptic 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

Lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. It is recommended that 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 studies in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9 % of patients randomised to lacosamide and 35.2 % of patients randomised 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 clinical studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomised to lacosamide and 1.6 % for patients randomised 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 study 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.

The safety profile of lacosamide reported in a study conducted in patients aged 4 years and older with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures (PGTCS) was consistent with the safety profile reported from the pooled placebo-controlled clinical studies in partial-onset seizures. Additional adverse reactions reported in PGTCS patients were myoclonic epilepsy (2.5 % in

the lacosamide-group and 0 % in the placebo-group) and ataxia (3.3 % in the lacosamide-group and 0 % in the placebo-group). The most frequently reported adverse reactions were dizziness and somnolence. The most common adverse reactions resulting in discontinuation of lacosamide therapy were dizziness and suicidal ideation. The discontinuation rate due to adverse reactions was 9.1 % in the lacosamide group and 4.1 % in the placebo group.

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical studies 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 Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt [1] Suicidal ideation Hallucination [1]	
Nervous system disorders	Dizziness Headache	Myoclonic seizures[3] Ataxia Balance disorder Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2] Coordination abnormal Dyskinesia	Convulsion
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		

System organ class	Very common	Common	Uncommon	Not known
Cardiac disorders			Atrioventricular block[1,2] Bradycardia[1,2] Atrial Fibrillation [1,2] Atrial Flutter [1,2]	Ventricular tachyarrhythmia [1]
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 [4] Irritation[4]	Erythema[4]	
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] Reported in PGTCS studies.
[4] 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 studies 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 study 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 studies 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 study 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 studies; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

Laboratory abnormalities
Abnormalities in liver function tests have been observed in placebo-controlled clinical studies with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic medicinal products. 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 medicinal products. 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

The safety profile of lacosamide in placebo-controlled (255 patients from 1 month to less than 4 years of age and 343 patients from 4 years to less than 17 years of age) and in open-label clinical studies (847 patients from 1 month to less than or equal to 18 years of age) in adjunctive therapy in paediatric patients with partial-onset seizures was consistent with the safety profile observed in adults. As data available in paediatric patients younger than 2 years of age is limited, lacosamide is not indicated in this age range.
The additional adverse reactions observed in the paediatric population were pyrexia, nasopharyngitis, pharyngitis, decreased appetite, abnormal behaviour and lethargy. Somnolence was reported more frequently in the paediatric population (≥ 1/10) compared to the adult population (≥ 1/100 to < 1/10).

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, diarrhoea 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 adult 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 adult 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 (generalised 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 generalised 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 (partial-onset seizures)
Adult population

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 generalisation. The patients were randomised 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 1,200 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, randomised study. 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 randomised to be converted to lacosamide monotherapy (either 400 mg/day or 300 mg/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, randomised, placebo-controlled clinical studies with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy studies, 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 studies, involving 1,308 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 antiepileptic medicinal products 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 intravenous lacosamide were determined in a multicenter, open-label study designed to assess the safety and tolerability of rapid initiation of lacosamide using a single intravenous loading dose (including 200 mg) followed by twice daily oral dosing (equivalent to the intravenous dose) as adjunctive therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

Paediatric population

Partial-onset seizures have a similar pathophysiology and clinical expression in children from 2 years of age and in adults. The efficacy of lacosamide in children aged 2 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).
The efficacy supported by the extrapolation principle stated above was confirmed by a double-blind, randomised, placebo-controlled clinical study. The study consisted of an 8-week baseline period followed by a 6-week titration period. Eligible patients on a stable dose regimen of 1 to ≤ 3 antiepileptic medicinal products, who still experienced at least 2 partial-onset seizures during the 4 weeks prior to screening with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the baseline period, were randomised to receive either placebo (n=172) or lacosamide (n=171).

Dosing was initiated at a dose of 2 mg/kg/day in subjects weighing less than 50 kg or 100 mg/day in subjects weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 1or 2 mg/kg/day increments in subjects weighing less than 50 kg or 50 or 100 mg/day in subjects weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose range.
Subjects must have achieved the minimum target dose for their body weight category for the final 3 days of the titration period to be eligible for entry into the 10-week maintenance period. Subjects were to remain on stable lacosamide dose throughout the maintenance period or were withdrawn and entered in the blinded taper period.
Statistically significant (p=0.0003) and clinically relevant reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was observed between the lacosamide and the placebo group. The percent reduction over placebo based on analysis of covariance was 31.72 % (95 % CI: 16.342,44.277).
Overall, the proportion of subjects with at least a 50 % reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was 52.9 % in the lacosamide group compared with 33.3 % in the placebo group.
The quality of life assessed by the Pediatric Quality of Life Inventory indicated that subjects in both lacosamide and placebo groups had a similar and stable health-related quality of life during the entire treatment period.

Clinical efficacy and safety (primary generalized tonic-clonic seizures)

The efficacy of lacosamide as adjunctive therapy in patients 4 years of age and older with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures (PGTCS) was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center clinical study. The study consisted of a 12-week historical baseline period, a 4-week prospective baseline period and a 24-week treatment period (which included a 6-week titration period and an 18-week maintenance period). Eligible patients on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTCS during the 16-week combined baseline period were randomized 1 to 1 to receive lacosamide or placebo (patients in the full analysis set: lacosamide n=118, placebo n=121; of them 8 patients in the ≥ 4 to < 12 years age group and 16 patients in the ≥ 12 to < 18 years range were treated with lacosamide and 9 and 16 patients, respectively with placebo).
Patients were titrated up to the target maintenance period dose of 12 mg/kg/day in patients weighing less than 30 kg, 8 mg/kg/day in patients weighing from 30 to less than 50 kg or 400 mg/day in patients weighing 50 kg or more.

Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Time to second PGTCS		
Median (days)	77.0	-
95 % CI	49.0, 128.0	-
Lacosamide – Placebo		
Hazard Ratio	0.540	
95 % CI	0.377, 0.774	
p-value	< 0.001	
Seizure freedom		
Stratified Kaplan-Meier estimate (%)	17.2	31.3
95 % CI	10.4, 24.0	22.8, 39.9
Lacosamide – Placebo	14.1	
95 % CI	3.2, 25.1	
p-value	0.011	

Note: For the lacosamide group, the median time to second PGTCS could not be estimated by Kaplan-Meier methods because > 50% of patients did not experience a second PGTCS by Day 166.

The findings in the paediatric subgroup were consistent with the results of the overall population for the primary, secondary and other efficacy endpoints.

5.2 Pharmacokinetic properties

Absorption

After intravenous administration, C_{max} is reached at the end of infusion. The plasma concentration increases proportionally with dose after oral (100-800 mg) and intravenous (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 lacosamide 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 study 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 faeces. The elimination half-life of lacosamide 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 studies 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 end-stage renal disease requiring haemodialysis 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 end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage 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).

Paediatric population
The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in six placebo-controlled randomised clinical studies and five open-label studies in 1655 adult and paediatric patients with epilepsy aged 1 month to 17 years. Three of these studies were performed in adults, 7 in pediatric patients, and 1 in a mixed population. The administered lacosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, not to exceed 600 mg/day.
The typical plasma clearance was estimated to be 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 10 kg, 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.74 L/h in adults (70 kg body weight).
Population pharmacokinetic analysis using sparse pharmacokinetic samples from PGTCS study showed a similar exposure in patients with PGTCS and in patients with partial-onset seizures.

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 anesthetised 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 anesthetised 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.
In juvenile rats and dogs, the types of toxicity do not differ qualitatively from those observed in adult animals. In juvenile rats, a reduced body weight was observed at systemic exposure levels similar to the expected clinical exposure. In juvenile dogs, transient and dose-related CNS clinical signs started to be observed at systemic exposure levels below the expected clinical exposure.

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 pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Product with particulate matter or discolouration should not be used.
This medicinal product is for single use only, any unused solution should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
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 S.A.
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: https://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

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

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

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

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 tablets
14 x 1 film-coated tablets
28 film-coated tablets
60 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 S.A.
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 tablets
EU/1/08/470/024 14 x 1 film-coated tablets
EU/1/08/470/025 28 film-coated tablets
EU/1/08/470/032 60 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 tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 50 mg film-coated tablets
<For 56 x 1 and 14 x 1 film-coated tablets> Vimpat 50 mg tablets
lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

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

60 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 S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 tablets
14 x 1 film-coated tablets
28 film-coated tablets
60 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 S.A.
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 tablets
EU/1/08/470/026 14 x 1 film-coated tablets
EU/1/08/470/027 28 film-coated tablets
EU/1/08/470/033 60 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 tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 100 mg film-coated tablets
<For 56 x 1 and 14 x 1 film-coated tablets> Vimpat 100 mg tablets
lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

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

60 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 S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/033

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 tablets
14 x 1 film-coated tablets
28 film-coated tablets
60 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 S.A.
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 tablets
EU/1/08/470/028 14 x 1 film-coated tablets
EU/1/08/470/029 28 film-coated tablets
EU/1/08/470/034 60 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 tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 150 mg film-coated tablets
<For 56 x 1 and 14 x 1 film-coated tablets> Vimpat 150 mg tablets
lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

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

60 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 S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/034

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 tablets
14 x 1 film-coated tablets
28 film-coated tablets
60 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 S.A.
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 tablets
EU/1/08/470/030 14 x 1 film-coated tablets
EU/1/08/470/031 28 film-coated tablets
EU/1/08/470/035 60 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 tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister label

1. NAME OF THE MEDICINAL PRODUCT

Vimpat 200 mg film-coated tablets
<For 56 x 1 and 14 x 1 film-coated tablets> Vimpat 200 mg tablets
lacosamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

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

60 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 S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/035

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TREATMENT INITIATION PACK ONLY

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TREATMENT INITIATION PACK ONLY

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 S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 1

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TREATMENT INITIATION PACK ONLY

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TREATMENT INITIATION PACK ONLY

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 S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 2

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TREATMENT INITIATION PACK ONLY

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TREATMENT INITIATION PACK ONLY

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 S.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Week 3

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TREATMENT INITIATION PACK ONLY

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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TREATMENT INITIATION PACK ONLY

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 S.A.

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 2,000 mg lacosamide.

3. LIST OF EXCIPIENTS

Contains sorbitol (E420), sodium methyl parahydroxybenzoate (E219), propylene glycol (E1520), sodium and aspartame (E951). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

200 ml syrup with 1 measuring cup (30 ml) and 1 oral syringe (10 ml) with 1 adaptor
Check with your doctor which device you should use.
30 ml measuring cup and 10 ml syringe *(as colored symbols - only for the outer carton)*

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. *(only for the outer carton)*
Oral use
Shake well before 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
After first opening, bottle may be used for up to 6 months.
Opening date *(only for the outer carton)*

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 S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium *(only for the outer carton)*

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/470/018

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)*

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. *(only for the outer carton)*

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

(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

Contains sodium chloride, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

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

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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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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

Contains sodium chloride, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

200 mg/20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

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B-1070 Bruxelles
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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.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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

What Vimpat is
Vimpat contains lacosamide. This belongs to a group of medicines called “antiepileptic medicines”. These medicines are used to treat epilepsy.
- You have been given this medicine to lower the number of fits (seizures) you have.

What Vimpat is used for
- Vimpat is used:
  - on its own and in association with other antiepileptic medicines in adults, adolescents and children aged 2 years and older to treat a certain type of epilepsy characterised by the occurrence of partial-onset seizure with or without secondary generalisation. In this type of epilepsy, fits first affect only one side of your brain. However, these may then spread to larger areas on both sides of your brain;
  - in association with other antiepileptic medicines in adults, adolescents and children aged 4 years and older to treat primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

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 have a certain type of heart beat problem called second- or third-degree AV block.

Do not take Vimpat if any of the above applies to you. If you are not sure, talk to your doctor or

pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor before taking Vimpat if:
- you have thoughts of harming or killing yourself. A small number of people being treated with antiepileptic medicinal products such as lacosamide have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, tell your doctor straight away.
- you have a heart problem that affects the beat of your heart and you often have a particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation and atrial flutter).
- you have severe heart disease such as heart failure or have had a heart attack.
- you are often dizzy or fall over. Vimpat may make you dizzy - this could increase the risk of accidental injury or a fall. This means that you should take care until you are used to the effects of this medicine.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.
If you are taking Vimpat, talk to your doctor if you are experiencing a new type of seizure or worsening of existing seizures.
If you are taking Vimpat and you are experiencing symptoms of abnormal heartbeat (such as slow, rapid or irregular heartbeat, palpitations, shortness of breath, feeling lightheaded, fainting), seek medical advice immediately (see section 4).

Children
Vimpat is not recommended for children aged under 2 years with epilepsy characterised by the occurrence of partial-onset seizure and not recommended for children aged under 4 years with primary generalised tonic-clonic seizures. This is because we do not yet know whether it will work and whether it is safe for children 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.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that affect your heart - this is because Vimpat can also affect your heart:
- medicines to treat heart problems;
- medicines which can increase the “PR interval” on a scan of the heart (ECG or electrocardiogram) such as medicines for epilepsy or pain called carbamazepine, lamotrigine or pregabalin;
- medicines used to treat certain types of irregular heart beat or heart failure.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.

Also tell your doctor or pharmacist if you are taking any of the following medicines - this is because they may increase or decrease the effect of Vimpat on your body:
- medicines for fungal infections such as fluconazole, itraconazole or ketoconazole;
- medicines for HIV such as ritonavir;
- medicines used to treat bacterial infections such as clarithromycin or rifampicin;
- a herbal medicine used to treat mild anxiety and depression called St. John’s wort.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.

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

Pregnancy and breast-feeding
Fertile women should discuss the use of contraceptives with the doctor.

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.
It is not recommended to breast-feed your baby while taking Vimpat, as Vimpat passes into breast milk.
Seek advice immediately from your doctor if you get pregnant or are planning to become pregnant. They will help you decide if you should take Vimpat or not.

Do not stop treatment without talking to your doctor first as this could increase your fits (seizures). A worsening of your disease can also harm your baby.

Driving and using machines
Do not drive, cycle or use any tools or machines until you know how this medicine affects you. This is because Vimpat may make you feel dizzy or cause blurred vision.

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. Other form(s) of this medicine may be more suitable for children; ask your doctor or pharmacist.

Taking Vimpat
- Take Vimpat twice each day - approximately 12 hours apart.
- Try to take it at about the same time each day.
- Swallow the Vimpat tablet with a glass of water.
- You may take Vimpat with or without food.

You will usually start by taking a low dose each day and your doctor will slowly increase this over a number of weeks. When you reach the dose that works for you, this is called the “maintenance dose”, you then take the same amount each day. Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

How much to take
Listed below are the normal recommended doses of Vimpat for different age groups and weights. Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

Adolescents and children weighing 50 kg or more and adults
<u>When you take Vimpat on its own</u>
- The usual starting dose of Vimpat is 50 mg twice a day.
- Your doctor may also prescribe a starting dose of 100 mg of Vimpat twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg. This will be until you reach a maintenance dose between 100 mg and 300 mg twice a day.

<u>When you take Vimpat with other antiepileptic medicines</u>
- The usual starting dose of Vimpat is 50 mg twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg. This will be until you reach a maintenance dose between 100 mg and 200 mg twice a day.

- If you weigh 50 kg or more, your doctor may decide to start Vimpat treatment with a single “loading” dose of 200 mg. You would then start your ongoing maintenance dose 12 hours later.

Children and adolescents weighing less than 50 kg
- *In the treatment of partial-onset seizure*: Observe that Vimpat is not recommended for children under 2 years of age.
- *In the treatment of primary generalised tonic-clonic seizures*: Observe that Vimpat is not recommended for children under 4 years of age.

- The dose depends on their body weight. They usually start treatment with the syrup and only change to tablets if they are able to take tablets and get the correct dose with the different tablet strengths. The doctor will prescribe the formulation that is best suited to them.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately. Do not try to drive. You may experience:
- dizziness;
- feeling sick (nausea) or being sick (vomiting);
- fits (seizures), heart beat problems such a slow, fast or irregular heart beat, coma or a fall in blood pressure with rapid heartbeat and sweating.

If you forget to take Vimpat
- If you have missed a dose within the first 6 hours of the scheduled dose, take it as soon as you remember.
- If you have missed a dose beyond the first 6 hours of the scheduled dose, do not take the missed tablet anymore. Instead 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 epilepsy may come back again or become worse.
- If your doctor decides to stop your treatment with Vimpat, they will tell you how to 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 single “loading” dose.

Talk to your doctor or pharmacist if you get any of the following:

Very common: may affect more than 1 in 10 people
- Headache;
- Feeling dizzy or sick (nausea);
- Double vision (diplopia).

Common: may affect up to 1 in 10 people
- Short jerks of a muscle or group of muscles (myoclonic seizures);
- Difficulties in coordinating your movements or walking;
- Problems in keeping your balance, shaking (tremor), tingling (paresthesia) or muscle spasms,

falling easily and getting bruises;
- Troubles with your memory, thinking or finding words, confusion;
- Rapid and uncontrollable movements of the eyes (nystagmus), blurred vision;
- A spinning sensation (vertigo), feeling drunk;
- Being sick (vomiting), dry mouth, constipation, indigestion, excessive gas in the stomach or bowel, diarrhoea;
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention;
- Noise in the ear such as buzzing, ringing or whistling;
- Irritability, trouble sleeping, depression;
- Sleepiness, tiredness or weakness (asthenia);
- Itching, rash.

Uncommon: may affect up to 1 in 100 people
- Slow heart rate, palpitations, irregular pulse or other changes in the electrical activity of your heart (conduction disorder);
- Exaggerated feeling of wellbeing, seeing and/or hearing things which are not there;
- Allergic reaction to medicine intake, hives;
- Blood tests may show abnormal liver function, liver injury;
- Thoughts of harming or killing yourself or attempting suicide: tell your doctor straight away;
- Feeling angry or agitated;
- Abnormal thinking or losing touch with reality;
- Serious allergic reaction which causes swelling of the face, throat, hands, feet, ankles, or lower legs;
- Fainting;
- Abnormal involuntary movements (dyskinesia).

Not known: frequency cannot be estimated from available data
- Abnormal rapid heartbeat (ventricular tachyarrhythmia);
- A sore throat, high temperature and getting more infections than usual. Blood tests may show a severe decrease in a specific class of white blood cells (agranulocytosis);
- A serious skin reaction which may include a high temperature and other flu-like symptoms, a rash on the face, extended rash, swollen glands (enlarged lymph nodes). Blood tests may show increased levels of liver enzymes and a type of white blood cell (eosinophilia);
- 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);
- Convulsion.

Additional side effects in children

The additional side effects in children were fever (pyrexia), runny nose (nasopharyngitis), sore throat (pharyngitis), eating less than usual (decreased appetite), changes in behaviour, not acting like themselves (abnormal behavior) and lacking in energy (lethargy). Feeling sleepy (somnolence) is a very common side effect in children and may affect more than 1 in 10 children.

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 medicine 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 of approximately 10.4 mm x 4.9 mm with a debossed ‘SP’ on one side and ‘50’ on the other side.
- Vimpat 100 mg are dark yellow, oval film-coated tablets of approximately 13.2 mm x 6.1 mm with a debossed ‘SP’ on one side and ‘100’ on the other side.
- Vimpat 150 mg are salmon, oval film-coated tablets of approximately 15.1 mm x 7.0 mm with a debossed ‘SP’ on one side and ‘150’ on the other side.
- Vimpat 200 mg are blue, oval film-coated tablets of approximately 16.6 mm x 7.8 mm with a debossed ‘SP’ on one side and ‘200’ on the other side.

Vimpat is available in packs of 14, 28, 56, 60, 14 x 1 and 56 x 1 film-coated tablets.
Vimpat 50 mg and Vimpat 100 mg are available in packs of 168 film-coated tablets and Vimpat 150 mg and Vimpat 200 mg are available in multipacks comprising 3 cartons, each containing 56 tablets. The 14 x 1 and 56 x 1 film-coated tablets packs are available as perforated unit dose PVC/PVDC blisters sealed with an aluminium foil, the 14, 28, 56 and 168 packs are available with standard PVC/PVDC blisters sealed with an aluminium foil, the 60 packs are available in HDPE bottles with a child-resistant closure. Not all pack sizes may be marketed.

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

Manufacturer
UCB Pharma S.A., Chemin du Foriest, B-1420 Braine-l'Alleud, Belgium.
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: https://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

The treatment initiation pack is only suitable in adolescents and children weighing 50 kg or more and in adults.

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

What Vimpat is
Vimpat contains lacosamide. This belongs to a group of medicines called “antiepileptic medicines”. These medicines are used to treat epilepsy.
- You have been given this medicine to lower the number of fits (seizures) you have.

What Vimpat is used for
- Vimpat is used:
  - on its own and in association with other antiepileptic medicines in adults, adolescents and children aged 2 years and older to treat a certain type of epilepsy characterised by the occurrence of partial-onset seizure with or without secondary generalisation. In this type of epilepsy, fits first affect only one side of your brain. However, these may then spread to larger areas on both sides of your brain;
  - in association with other antiepileptic medicines in adults, adolescents and children aged 4 years and older to treat primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

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 have a certain type of heart beat problem called second- or third-degree AV block.

Do not take Vimpat if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor before taking Vimpat if:
- you have thoughts of harming or killing yourself. A small number of people being treated with antiepileptic medicinal products such as lacosamide have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, tell your doctor straight away.
- you have a heart problem that affects the beat of your heart and you often have a particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation and atrial flutter).
- you have severe heart disease such as heart failure or have had a heart attack.
- you are often dizzy or fall over. Vimpat may make you dizzy - this could increase the risk of accidental injury or a fall. This means that you should take care until you are used to the effects of this medicine.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.
If you are taking Vimpat, talk to your doctor if you are experiencing a new type of seizure or worsening of existing seizures.
If you are taking Vimpat and you are experiencing symptoms of abnormal heartbeat (such as slow, rapid or irregular heartbeat, palpitations, shortness of breath, feeling lightheaded, fainting), seek medical advice immediately (see section 4).

Children
Vimpat is not recommended for children aged under 2 years with epilepsy characterised by the occurrence of partial-onset seizure and not recommended for children aged under 4 years with primary generalised tonic-clonic seizures. This is because we do not yet know whether it will work and whether it is safe for children 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.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that affect your heart - this is because Vimpat can also affect your heart:
- medicines to treat heart problems;
- medicines which can increase the “PR interval” on a scan of the heart (ECG or electrocardiogram) such as medicines for epilepsy or pain called carbamazepine, lamotrigine or pregabalin;
- medicines used to treat certain types of irregular heart beat or heart failure.

If any of the above apply to you (or you are not sure) talk to your doctor or pharmacist before taking Vimpat.

Also tell your doctor or pharmacist if you are taking any of the following medicines - this is because they may increase or decrease the effect of Vimpat on your body:
- medicines for fungal infections such as fluconazole, itraconazole or ketoconazole;
- medicines for HIV such as ritonavir;
- medicines for bacterial infections such as clarithromycin or rifampicin;
- a herbal medicine used to treat mild anxiety and depression called St. John’s wort.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.

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

Pregnancy and breast-feeding
Fertile women should discuss the use of contraceptives with the doctor.

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.
It is not recommended to breast-feed your baby while taking Vimpat, as Vimpat passes into breast milk.
Seek advice immediately from your doctor if you get pregnant or are planning to become pregnant. They will help you decide if you should take Vimpat or not.

Do not stop treatment without talking to your doctor first as this could increase your fits (seizures). A worsening of your disease can also harm your baby.

Driving and using machines
Do not drive, cycle or use any tools or machines until you know how this medicine affects you. This is because Vimpat may make you feel dizzy or cause blurred vision.

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. Other form(s) of this medicine may be more suitable for children; ask your doctor or pharmacist.

Taking Vimpat
- Take Vimpat twice each day - approximately 12 hours apart.
- Try to take it at about the same time each day.
- Swallow the Vimpat tablet with a glass of water.
- You may take Vimpat with or without food.

You will usually start by taking a low dose each day and your doctor will slowly increase this over a number of weeks. When you reach the dose that works for you, this is called the “maintenance dose”, you then take the same amount each day. Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

How much to take
Listed below are the normal recommended doses of Vimpat for different age groups and weights. Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

Adolescents and children weighing 50 kg or more and adults only
When you take Vimpat on its own
The usual starting dose of Vimpat is 50 mg twice a day.
Your doctor may also prescribe a starting dose of 100 mg of Vimpat twice a day.

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

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 (1 tablet 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.

Children and adolescents below 50 kg
The treatment initiation pack is not suitable for children and adolescents weighing less than 50 kg.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately. Do not try to drive. You may experience:
- dizziness;
- feeling sick (nausea) or being sick (vomiting);
- fits (seizures), heart beat problems such as a slow, fast or irregular heart beat, coma or a fall in blood pressure with rapid heartbeat and sweating.

If you forget to take Vimpat
- If you have missed a dose within the first 6 hours of the scheduled dose, take it as soon as you remember.
- If you have missed a dose beyond the first 6 hours of the scheduled dose, do not take the missed tablet anymore. Instead 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 epilepsy may come back again or become worse.
- If your doctor decides to stop your treatment with Vimpat, they will tell you how to 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.

Talk to your doctor or pharmacist if you get any of the following:

Very common: may affect more than 1 in 10 people
- Headache;
- Feeling dizzy or sick (nausea);
- Double vision (diplopia).

Common: may affect up to 1 in 10 people
- Short jerks of a muscle or group of muscles (myoclonic seizures);
- Difficulties in coordinating your movements or walking;
- Problems in keeping your balance, shaking (tremor), tingling (paresthesia) or muscle spasms, falling easily and getting bruises;
- Troubles with your memory, thinking or finding words, confusion;
- Rapid and uncontrollable movements of the eyes (nystagmus), blurred vision;
- A spinning sensation (vertigo), feeling drunk;
- Being sick (vomiting), dry mouth, constipation, indigestion, excessive gas in the stomach or bowel, diarrhoea;
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention;
- Noise in the ear such as buzzing, ringing or whistling;
- Irritability, trouble sleeping, depression;
- Sleepiness, tiredness, or weakness (asthenia);
- Itching, rash.

Uncommon: may affect up to 1 in 100 people
- Slow heart rate, palpitations, irregular pulse or other changes in the electrical activity of your heart (conduction disorder);
- Exaggerated feeling of wellbeing, seeing and/or hearing things which are not there;
- Allergic reaction to medicine intake, hives;
- Blood tests may show abnormal liver function, liver injury;
- Thoughts of harming or killing yourself or attempting suicide: tell your doctor straight away;
- Feeling angry or agitated;
- Abnormal thinking or losing touch with reality;
- Serious allergic reaction which causes swelling of the face, throat, hands, feet, ankles, or lower legs;
- Fainting;
- Abnormal involuntary movements (dyskinesia).

Not known: frequency cannot be estimated from available data
- Abnormal rapid heartbeat (ventricular tachyarrhythmia);
- A sore throat, high temperature and getting more infections than usual. Blood tests may show a severe decrease in a specific class of white blood cells (agranulocytosis);
- A serious skin reaction which may include a high temperature and other flu-like symptoms, a rash on the face, extended rash, swollen glands (enlarged lymph nodes). Blood tests may show increased levels of liver enzymes and a type of white blood cell (eosinophilia);
- 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);
- Convulsion.

Additional side effects in children

The additional side effects in children were fever (pyrexia), runny nose (nasopharyngitis), sore throat (pharyngitis), eating less than usual (decreased appetite), changes in behaviour, not acting like themselves (abnormal behavior) and lacking in energy (lethargy). Feeling sleepy (somnolence) is a very common side effect in children and may affect more than 1 in 10 children.

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.

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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 medicine 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.
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  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 of approximately 10.4 mm x 4.9 mm with a debossed ‘SP’ on one side and ‘50’ on the other side.
- Vimpat 100 mg are dark yellow, oval film-coated tablets of approximately 13.2 mm x 6.1 mm with a debossed ‘SP’ on one side and ‘100’ on the other side.
- Vimpat 150 mg are salmon, oval film-coated tablets of approximately 15.1 mm x 7.0 mm with

a debossed ‘SP’ on one side and ‘150’ on the other side.
- Vimpat 200 mg are blue, oval film-coated tablets of approximately 16.6 mm x 7.8 mm 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
UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium.

Manufacturer
UCB Pharma S.A., Chemin du Foriest, B-1420 Braine-l’Alleud, Belgium.
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: https://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 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

What Vimpat is
Vimpat contains lacosamide. This belongs to a group of medicines called “antiepileptic medicines”. These medicines are used to treat epilepsy.
- You have been given this medicine to lower the number of fits (seizures) you have.

What Vimpat is used for
- Vimpat is used:
  - on its own and in association with other antiepileptic medicines in adults, adolescents and children aged 2 years and older to treat a certain type of epilepsy characterised by the occurrence of partial-onset seizure with or without secondary generalisation. In this type of epilepsy, fits first affect only one side of your brain. However, these may then spread to larger areas on both sides of your brain;
  - in association with other antiepileptic medicines in adults, adolescents and children aged 4 years and older to treat primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

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 have a certain type of heart beat problem called second- or third-degree AV block.

Do not take Vimpat if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor before taking Vimpat if:
- you have thoughts of harming or killing yourself. A small number of people being treated with antiepileptic medicinal products such as lacosamide have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, tell your doctor straight away.
- you have a heart problem that affects the beat of your heart and you often have a particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation or atrial flutter).
- you have severe heart disease such as heart failure or have had a heart attack.
- you are often dizzy or fall over. Vimpat may make you dizzy – this could increase the risk of accidental injury or a fall. This means that you should take care until you are used to the effects of this medicine.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.
If you are taking Vimpat, talk to your doctor if you are experiencing a new type of seizure or worsening of existing seizures.
If you are taking Vimpat and you are experiencing symptoms of abnormal heartbeat (such as slow, rapid or irregular heartbeat, palpitations, shortness of breath, feeling lightheaded, fainting), seek medical advice immediately (see section 4).

Children
Vimpat is not recommended for children aged under 2 years with epilepsy characterised by the occurrence of partial-onset seizure and not recommended for children aged under 4 years with primary generalised tonic-clonic seizures. This is because we do not yet know whether it will work and whether it is safe for children 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.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that affect your heart - this is because Vimpat can also affect your heart:
- medicines to treat heart problems;
- medicines which can increase the “PR interval” on a scan of the heart (ECG or electrocardiogram) such as medicines for epilepsy or pain called carbamazepine, lamotrigine or pregabalin;
- medicines used to treat certain types of irregular heart beat or heart failure.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.

Also tell your doctor or pharmacist if you are taking any of the following medicines - this is because they may increase or decrease the effect of Vimpat on your body:
- medicines for fungal infections such as fluconazole, itraconazole or ketoconazole;
- medicines for HIV such as ritonavir;
- medicines for bacterial infections such as clarithromycin or rifampicin;
- a herbal medicine used to treat mild anxiety and depression called St. John’s wort.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Vimpat.

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

Pregnancy and breast-feeding
Fertile women should discuss the use of contraceptives with the doctor.

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.
It is not recommended to breast-feed your baby while taking Vimpat, as Vimpat passes into breast milk.
Seek advice immediately from your doctor if you get pregnant or are planning to become pregnant. They will help you decide if you should take Vimpat or not.

Do not stop treatment without talking to your doctor first as this could increase your fits (seizures). A worsening of your disease can also harm your baby.

Driving and using machines
Do not drive, cycle or use any tools or machines until you know how this medicine affects you. This is because Vimpat may make you feel dizzy or cause blurred vision.

Vimpat contains sorbitol, sodium, sodium methyl parahydroxybenzoate, aspartame, propylene glycol and potassium
- Sorbitol (a type of sugar): This medicine contains 187 mg sorbitol in each ml. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
- Sodium (salt): This medicine contains 1.42 mg sodium (main component of cooking/table salt) in each ml. This is equivalent to 0.07 % of the recommended maximum daily dietary intake of sodium for an adult.
- Sodium methyl parahydroxybenzoate (E219) may cause allergic reactions (possibly delayed).
- Aspartame (E951): This medicine contains 0.032 mg aspartame in each ml. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.
- Propylene glycol (E1520): This medicine contains 2.14 mg propylene glycol in each ml.
- Potassium: This medicine contains potassium, less than 1 mmol (39 mg) per 60 ml, i.e. essentially 'potassium-free'.

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.

Taking Vimpat
- Take Vimpat twice each day - approximately 12 hours apart.
- Try to take it at about the same time each day.
- You may take Vimpat with or without food.

You will usually start by taking a low dose each day and your doctor will slowly increase this over a number of weeks. When you reach the dose that works for you, this is called the “maintenance dose”, you then take the same amount each day. Vimpat is used as a long term treatment. You should continue to take Vimpat until your doctor tells you to stop.

How much to take
Listed below are the normal recommended doses of Vimpat for different age groups and weights. Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

Use the 10 ml oral syringe (black graduation marks) or the 30 ml measuring cup provided in the carton box, as appropriate, according to the dosage required. See instructions for use below.

Adolescents and children weighing 50 kg or more and adults

When you take Vimpat on its own
- The usual starting dose of Vimpat is 50 mg (5 ml) twice a day.
- Your doctor may also prescribe a starting dose of 100 mg (10 ml) of Vimpat twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg (5 ml). This will be until you reach a maintenance dose of between 100 mg (10 ml) and 300 mg (30 ml) twice a day.

When you take Vimpat with other antiepileptic medicines
- The usual starting dose of Vimpat is 50 mg (5 ml) twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg (5 ml). This will be until you reach a maintenance dose of between 100 mg (10 ml) and 200 mg (20 ml) twice a day.
- If you weigh 50 kg or more, your doctor may decide to start Vimpat treatment with a single “loading” dose of 200 mg (20 ml). You would then start your ongoing maintenance dose 12 hours later.

Children and adolescents weighing less than 50 kg
- *In the treatment of partial-onset seizure*: Observe that Vimpat is not recommended for children under 2 years of age.
- *In the treatment of primary generalised tonic-clonic seizures*: Observe that Vimpat is not recommended for children under 4 years of age.

When you take Vimpat on its own
- Your doctor will decide the dose of Vimpat based on your body weight.
- The usual starting dose is 1 mg (0.1 ml), for each kilogram (kg) of body weight, twice a day.
- Your doctor may then increase your twice daily dose every week by 1 mg (0.1 ml), for each kg of your body weight. This will be until you reach a maintenance dose.
- Dosing charts including the maximum recommended dose are provided below. This is for information only. Your doctor will work out the right dose for you.

To be taken twice daily for children from 2 years of age **weighing from 10 kg to less than 40 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 0.5 ml/kg	Week 6 Maximum recommended dose: 0.6 ml/kg
Use the 10 ml syringe (black graduation marks) for volume between 1 ml and 20 ml * Use the 30 ml measuring cup for volume more than 20 ml						
10 kg	1 ml	2 ml	3 ml	4 ml	5 ml	6 ml
15 kg	1.5 ml	3 ml	4.5 ml	6 ml	7.5 ml	9 ml
20 kg	2 ml	4 ml	6 ml	8 ml	10 ml	12 ml
25 kg	2.5 ml	5 ml	7.5 ml	10 ml	12.5 ml	15 ml
30 kg	3 ml	6 ml	9 ml	12 ml	15 ml	18 ml
35 kg	3.5 ml	7 ml	10.5 ml	14 ml	17.5 ml	21 ml*

To be taken twice daily for children and adolescents **weighing from 40 kg to less than 50 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 Maximum recommended dose: 0.5 ml/kg
Use the 10 ml syringe (black graduation marks) for volume between 1 ml and 20 ml * Use the 30 ml measuring cup for volume more than 20 ml					
40 kg	4 ml	8 ml	12 ml	16 ml	20 ml
45 kg	4.5 ml	9 ml	13.5 ml	18 ml	22.5 ml*

When you take Vimpat with other antiepileptic medicines

- Your doctor will decide the dose of Vimpat based on your body weight.
- The usual starting dose is 1 mg (0.1 ml), for each kilogram (kg) of body weight, twice a day.
- Your doctor may then increase your twice daily dose every week by 1 mg (0.1 ml) for each kg of body weight. This will be until you reach a maintenance dose.
- Dosing charts including the maximum recommended dose are provided below. This is for information only. Your doctor will work out the right dose for you.

To be taken twice daily for children from 2 years of age **weighing from 10 kg to less than 20 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 0.5 ml/kg	Week 6 Maximum recommended dose: 0.6 ml/kg
Use the 10 ml syringe (black graduation marks) for volume between 1 ml and 20 ml						
10 kg	1 ml	2 ml	3 ml	4 ml	5 ml	6 ml
12 kg	1.2 ml	2.4 ml	3.6 ml	4.8 ml	6 ml	7.2 ml
14 kg	1.4 ml	2.8 ml	4.2 ml	5.6 ml	7 ml	8.4 ml
15 kg	1.5 ml	3 ml	4.5 ml	6 ml	7.5 ml	9 ml
16 kg	1.6 ml	3.2 ml	4.8 ml	6.4 ml	8 ml	9.6 ml
18 kg	1.8 ml	3.6 ml	5.4 ml	7.2 ml	9 ml	10.8 ml

To be taken twice daily for children and adolescents **weighing from 20 kg to less than 30 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 Maximum recommended dose: 0.5 ml/kg
Use the 10 ml syringe (black graduation marks) for volume between 1 ml and 20 ml					
20 kg	2 ml	4 ml	6 ml	8 ml	10 ml
22 kg	2.2 ml	4.4 ml	6.6 ml	8.8 ml	11 ml
24 kg	2.4 ml	4.8 ml	7.2 ml	9.6 ml	12 ml
25 kg	2.5 ml	5 ml	7.5 ml	10 ml	12.5 ml
26 kg	2.6 ml	5.2 ml	7.8 ml	10.4 ml	13 ml
28 kg	2.8 ml	5.6 ml	8.4 ml	11.2 ml	14 ml

To be taken twice daily for children and adolescents **weighing from 30 kg to less than 50 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 Maximum recommended dose: 0.4 ml/kg
Use the 10 ml syringe (black graduation marks) for volume between 1 ml and 20 ml				
30 kg	3 ml	6 ml	9 ml	12 ml
35 kg	3.5 ml	7 ml	10.5 ml	14 ml
40 kg	4 ml	8 ml	12 ml	16 ml
45 kg	4.5 ml	9 ml	13.5 ml	18 ml

Instructions for use

It is important that you use the correct device to measure your dose. Your doctor or pharmacist will let you know which device to use depending on the dose that has been prescribed.

10 ml oral dosing syringe	**30 ml measuring cup**
The 10 ml oral syringe has black graduations in steps of 0.25 ml. If the required dose is between 1 ml and 10 ml, you should use the 10 ml oral syringe and the adaptor provided in this pack. If the required dose is between 10 ml and 20 ml, you will need to use the 10 ml syringe two times.	The 30 ml measuring cup has graduations in steps of 5 ml. If the required dose is above 20 ml, you should use the 30 ml measuring cup provided in this pack.

Instructions for use: measuring cup

1. Shake the bottle well before use.
2. Fill the measuring cup to the millilitre (ml) dose marker prescribed by your doctor.
3. Swallow the dose of syrup.
4. Then drink some water.

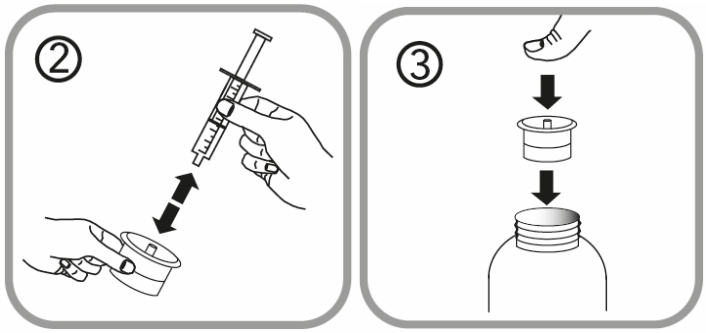
Instructions for use: oral syringe

Your doctor will show you how to use the oral syringe, before you use it for the first time. If you have any questions, please go back to your doctor or pharmacist.

Shake the bottle well before use.
Open the bottle by pressing the cap while turning it anti-clockwise (figure 1).

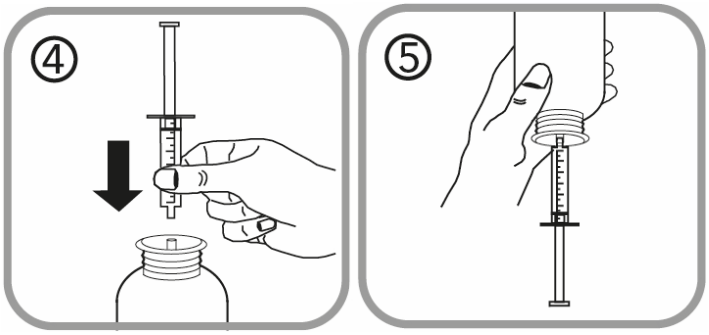
Follow these steps the first time you take Vimpat:

- Take off the adaptor from the oral syringe (figure 2).
- Put the adaptor into the top of the bottle (figure 3). Make sure it is fixed well in place. You do not need to remove the adaptor after use.



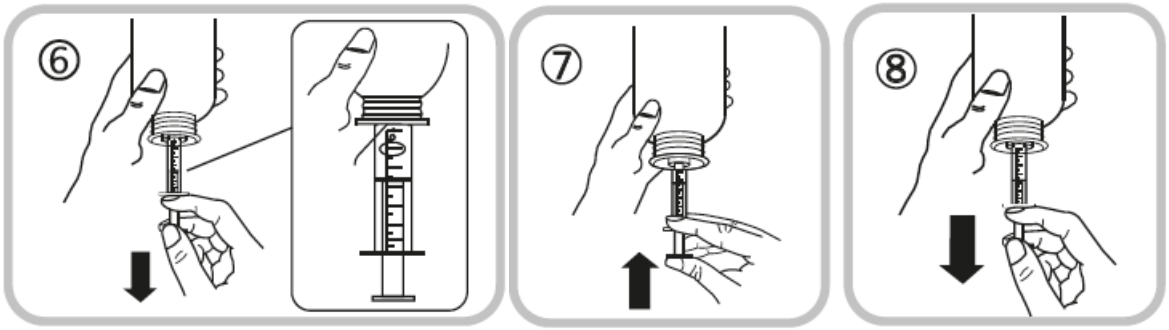
Follow these steps each time you take Vimpat:

- Put the oral syringe into the adaptor opening (figure 4).
- Turn the bottle upside down (figure 5).

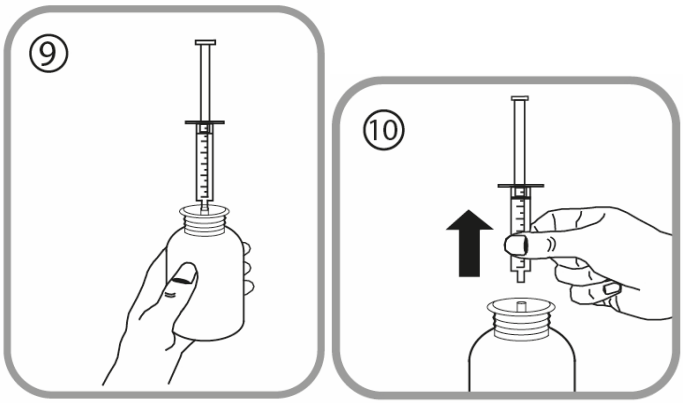


- Hold the bottle upside down in one hand and use the other hand to fill the oral syringe.
- Pull the plunger down to fill the oral syringe with a small amount of solution (figure 6).
- Push the plunger up to get rid of any bubbles (figure 7).

- Pull the plunger down to the millilitre (ml) dose marker prescribed by your doctor (figure 8). The plunger may rise back up the barrel on the first dosage. Therefore, ensure that the plunger is kept in position until the oral syringe is disconnected from the bottle.

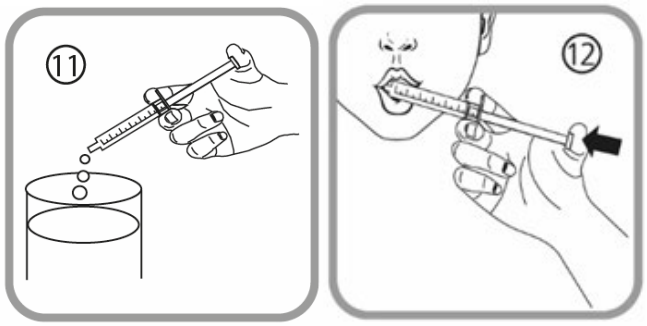


- Turn the bottle the right way up (figure 9).
- Take the oral syringe out of the adaptor (figure 10).

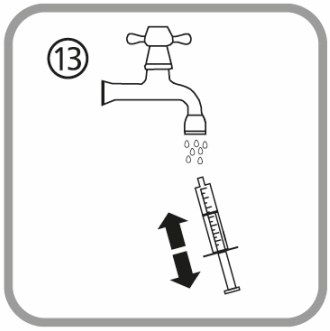


There are two ways in which you can choose to drink the medicine:

- empty the contents of the oral syringe into a little water by pushing the plunger to the bottom of the oral syringe (figure 11) – you will then need to drink all of the water (add just enough to make it easy to drink) **or**
- drink the solution directly from the oral syringe without water (figure 12) – drink the whole contents of the oral syringe.



- Close the bottle with the plastic screw cap (you do not need to remove the adaptor).
- To clean the oral syringe, rinse with cold water only, moving the plunger several times up and down to take up and expel the water, without separating the two components of the syringe (figure 13).



- Keep the bottle, the oral syringe, and the leaflet in the carton.

If you take more Vimpat than you should
If you have taken more Vimpat than you should, contact your doctor immediately. Do not try to drive. You may experience:
- dizziness;
- feeling sick (nausea) or being sick (vomiting);
- fits (seizures), heart beat problems such as a slow, fast or irregular heart beat, coma or a fall in blood pressure with rapid heartbeat and sweating.

If you forget to take Vimpat
- If you have missed a dose within the first 6 hours of the scheduled dose, take it as soon as you remember.
- If you have missed a dose beyond the first 6 hours of the scheduled dose, do not take the missed syrup anymore. Instead 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 epilepsy may come back again or become worse.
- If your doctor decides to stop your treatment with Vimpat, they will tell you how to 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 single “loading” dose.

Talk to your doctor or pharmacist if you get any of the following:

Very common: may affect more than 1 in 10 people
- Headache;
- Feeling dizzy or sick (nausea);
- Double vision (diplopia).

Common: may affect up to 1 in 10 people
- Short jerks of a muscle or group of muscles (myoclonic seizures);
- Difficulties in coordinating your movements or walking;
- Problems in keeping your balance, shaking (tremor), tingling (paresthesia) or muscle spasms, falling easily and getting bruises;
- Trouble with your memory, thinking or finding words, confusion;
- Rapid and uncontrollable movements of the eyes (nystagmus), blurred vision;
- A spinning sensation (vertigo), feeling drunk;
- Being sick (vomiting), dry mouth, constipation, indigestion, excessive gas in the stomach or bowel, diarrhoea;
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention;
- Noise in the ear such as buzzing, ringing or whistling;
- Irritability, trouble sleeping, depression;
- Sleepiness, tiredness or weakness (asthenia);
- Itching, rash.

Uncommon: may affect up to 1 in 100 people
- Slow heart rate, palpitations, irregular pulse or other changes in the electrical activity of your heart (conduction disorder);
- Exaggerated feeling of wellbeing, seeing and/or hearing things which are not there;
- Allergic reaction to medicine intake, hives;
- Blood tests may show abnormal liver function, liver injury;
- Thoughts of harming or killing yourself or attempting suicide: tell your doctor straight away;
- Feeling angry or agitated;
- Abnormal thinking or losing of touch with reality;
- Serious allergic reaction which causes swelling of the face, throat, hands, feet, ankles, or lower legs;
- Fainting;
- Abnormal involuntary movements (dyskinesia).

Not known: frequency cannot be estimated from available data
- Abnormal rapid heartbeat (ventricular tachyarrhythmia);
- A sore throat, high temperature and getting more infections than usual. Blood tests may show a severe decrease in a specific class of white blood cells (agranulocytosis);
- A serious skin reaction which may include a high temperature and other flu-like symptoms, a rash on the face, extended rash, swollen glands (enlarged lymph nodes). Blood tests may show increased levels of liver enzymes and a type of white blood cell (eosinophilia);
- 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);
- Convulsion.

Additional side effects in children

The additional side effects in children were fever (pyrexia), runny nose (nasopharyngitis), sore throat (pharyngitis), eating less than usual (decreased appetite), changes in behaviour, not acting like themselves (abnormal behavior) and lacking in energy (lethargy). Feeling sleepy (somnolence) is a very common side effect in children and may affect more than 1 in 10 children.

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, do not use beyond 6 months.

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, citric 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 a bottle of 200 ml.

The carton boxes of Vimpat syrup contain a 30 ml polypropylene measuring cup and a 10 ml polyethylene / polypropylene oral syringe (black graduation marks) with its polyethylene adaptor.
- The measuring cup is suitable for doses above 20 ml. Each graduation mark (5 ml) of the measuring cup corresponds to 50 mg of lacosamide (for example 2 graduation marks correspond to 100 mg).
- The 10 ml oral syringe is suitable for doses between 1 ml and 20 ml. One full 10 ml oral syringe corresponds to 100 mg of lacosamide. The minimum extractable volume is 1 ml, which is 10 mg of lacosamide. After this, each graduation mark (0.25 ml) corresponds to 2.5 mg of lacosamide (for example 4 graduation marks corresponds to 10 mg).

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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: https://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

What Vimpat is
Vimpat contains lacosamide. This belongs to a group of medicines called “antiepileptic medicines”. These medicines are used to treat epilepsy.
- You have been given this medicine to lower the number of fits (seizures) you have.

What Vimpat is used for
- Vimpat is used:
  - on its own and in association with other antiepileptic medicines in adults, adolescents and children aged 2 years and older to treat a certain type of epilepsy characterised by the occurrence of partial-onset seizure with or without secondary generalisation. In this type of epilepsy, fits first affect only one side of your brain. However, these may then spread to larger areas on both sides of your brain;
  - in association with other antiepileptic medicines in adults, adolescents and children aged 4 years and older to treat primary generalised tonic-clonic seizures (major fits, including loss of consciousness) in patients with idiopathic generalised epilepsy (the type of epilepsy that is thought to have a genetic cause).

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 have a certain type of heart beat problem called second- or third-degree AV block.

Do not use Vimpat if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before using this medicine.

Warnings and precautions
Talk to your doctor before using Vimpat if:
- you have thoughts of harming or killing yourself. A small number of people being treated with antiepileptic medicinal products such as lacosamide have had thoughts of harming or killing themselves. If you have any of these thoughts at any time, tell your doctor straight away.
- you have a heart problem that affects the beat of your heart and you often have a particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation and atrial flutter).
- you have severe heart disease such as heart failure or have had a heart attack.
- you are often dizzy or fall over. Vimpat may make you dizzy - this could increase the risk of accidental injury or a fall. This means that you should take care until you are used to the effects of this medicine.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using Vimpat.
If you are taking Vimpat, talk to your doctor if you are experiencing a new type of seizure or worsening of existing seizures.
If you are taking Vimpat and you are experiencing symptoms of abnormal heartbeat (such as slow, rapid or irregular heartbeat, palpitations, shortness of breath, feeling lightheaded, fainting), seek medical advice immediately (see section 4).

Children
Vimpat is not recommended for children aged under 2 years with epilepsy characterised by the occurrence of partial-onset seizure and not recommended for children aged under 4 years with primary generalised tonic-clonic seizures. This is because we do not yet know whether it will work and whether it is safe for children 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.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that affect your heart - this is because Vimpat can also affect your heart:
- medicines to treat heart problems;
- medicines which can increase the “PR interval” on a scan of the heart (ECG or electrocardiogram) such as medicines for epilepsy or pain called carbamazepine, lamotrigine or pregabalin;
- medicines used to treat certain types of irregular heart beat or heart failure.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using Vimpat.

Also tell your doctor or pharmacist if you are taking any of the following medicines - this is because they may increase or decrease the effect of Vimpat on your body:
- medicines for fungal infections such as fluconazole, itraconazole or ketoconazole;
- a medicine for HIV such as ritonavir;
- medicines for bacterial infections such as clarithromycin or rifampicin;
- a herbal medicine used to treat mild anxiety and depression called St. John’s wort.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before using Vimpat.

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

Pregnancy and breast-feeding
Fertile women should discuss the use of contraceptives with the doctor.

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 using this medicine.

It is not recommended to use Vimpat if you are pregnant, as the effects of Vimpat on pregnancy and the unborn baby are not known.
It is not recommended to breast-feed your baby while taking Vimpat, as Vimpat passes into breast milk.
Seek advice immediately from your doctor if you get pregnant or are planning to become pregnant. They will help you decide if you should use Vimpat or not.

Do not stop treatment without talking to your doctor first as this could increase your fits (seizures). A worsening of your disease can also harm your baby.

Driving and using machines
Do not drive, cycle or use any tools or machines until you know how this medicine affects you. This is because Vimpat may make you feel dizzy or cause blurred vision.

Vimpat contains sodium
This medicine contains 59.8 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Vimpat

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

Using Vimpat
- Vimpat can be started by:
  - taking the medicine by mouth or
  - by being given as an intravenous infusion (sometimes called an “IV infusion”) where the medicine is given into your vein by a doctor or nurse. It is given over 15 to 60 minutes.
- The IV infusion is usually used for a short time when you cannot take the medicine by mouth.
- Your doctor will decide for how many days you will have infusions. There is experience with twice daily infusions of Vimpat for up to 5 days. For longer term treatment Vimpat tablets and syrup are available.

When you change from the infusion to taking the medicine by mouth (or the other way around) the total amount you take each day and how often you take it stays the same.
- Use Vimpat twice each day (approximately 12 hours apart).
- Try to use it at about the same time each day.

How much to use
Listed below are the normal recommended doses of Vimpat for different age groups and weights. Your doctor may prescribe a different dose if you have problems with your kidneys or with your liver.

Adolescents and children weighing 50 kg or more and adults

When you use Vimpat on its own

- The usual starting dose of Vimpat is 50 mg twice a day.
- The treatment with Vimpat may also start with a dose of 100 mg of Vimpat twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg. This will be until you reach a maintenance dose of between 100 mg and 300 mg twice a day.

When you use Vimpat with other antiepileptic medicines

- The usual starting dose of Vimpat is 50 mg twice a day.
- Your doctor may increase your twice daily dose every week by 50 mg. This will be until you reach a maintenance dose of between 100 mg and 200 mg twice a day.
- If you weigh 50 kg or more, your doctor may decide to start Vimpat treatment with a single "loading" dose of 200 mg. You would then start your ongoing maintenance dose 12 hours later.

Children and adolescents weighing less than 50 kg

- *In the treatment of partial-onset seizure*: Observe that Vimpat is not recommended for children under 2 years of age.
- *In the treatment of primary generalised tonic-clonic seizures*: Observe that Vimpat is not recommended for children under 4 years of age.

When you use Vimpat on its own

- Your doctor will decide the dose of Vimpat based on your body weight.
- The usual starting dose is 1 mg (0.1 ml), for each kilogram (kg) of body weight, twice a day.
- Your doctor may then increase your twice daily dose every week by 1 mg (0.1 ml), for each kg of your body weight. This will be until you reach a maintenance dose.
- Dosing charts including the maximum recommended dose are provided below. This is for information only. Your doctor will work out the right dose for you.

To **be used twice daily** for children from 2 years of age **weighing from 10 kg to less than 40 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 0.5 ml/kg	Week 6 Maximum recommended dose: 0.6 ml/kg
10 kg	1 ml	2 ml	3 ml	4 ml	5 ml	6 ml
15 kg	1.5 ml	3 ml	4.5 ml	6 ml	7.5 ml	9 ml
20 kg	2 ml	4 ml	6 ml	8 ml	10 ml	12 ml
25 kg	2.5 ml	5 ml	7.5 ml	10 ml	12.5 ml	15 ml
30 kg	3 ml	6 ml	9 ml	12 ml	15 ml	18 ml
35 kg	3.5 ml	7 ml	10.5 ml	14 ml	17.5 ml	21 ml

To be used twice daily for children and adolescents **weighing from 40 kg to less than 50 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 Maximum recommended dose: 0.5 ml/kg
40 kg	4 ml	8 ml	12 ml	16 ml	20 ml
45 kg	4.5 ml	9 ml	13.5 ml	18 ml	22.5 ml

When you use Vimpat with other antiepileptic medicines

- Your doctor will decide the dose of Vimpat based on your body weight.
- For children and adolescents weighing from 10 kg to less than 50 kg, the usual starting dose is 1 mg (0.1 ml), for each kilogram (kg) of body weight, twice a day.
- Your doctor may then increase your twice daily dose every week by 1 mg (0.1 ml) for each kg of body weight. This will be until you reach a maintenance dose.
- Dosing charts including the maximum recommended dose are provided below. This is for information only. Your doctor will work out the right dose for you.

To be used twice daily for children from 2 years of age **weighing from 10 kg to less than 20 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 0.5 ml/kg	Week 6 Maximum recommended dose: 0.6 ml/kg
10 kg	1 ml	2 ml	3 ml	4 ml	5 ml	6 ml
15 kg	1.5 ml	3 ml	4.5 ml	6 ml	7.5 ml	9 ml

To be used twice daily for children and adolescents **weighing from 20 kg to less than 30 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 0.4 ml/kg	Week 5 Maximum recommended dose: 0.5 ml/kg
20 kg	2 ml	4 ml	6 ml	8 ml	10 ml
25 kg	2.5 ml	5 ml	7.5 ml	10 ml	12.5 ml

To be used twice daily for children and adolescents **weighing from 30 kg to less than 50 kg**

Weight	Week 1 Starting dose: 0.1 ml/kg	Week 2 0.2 ml/kg	Week 3 0.3 ml/kg	Week 4 Maximum recommended dose: 0.4 ml/kg
30 kg	3 ml	6 ml	9 ml	12 ml
35 kg	3.5 ml	7 ml	10.5 ml	14 ml
40 kg	4 ml	8 ml	12 ml	16 ml
45 kg	4.5 ml	9 ml	13.5 ml	18 ml

If you stop using Vimpat

If your doctor decides to stop your treatment with Vimpat, they will decrease the dose step by step. This is to prevent your epilepsy 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 single “loading” dose.

Talk to your doctor or pharmacist if you get any of the following:

Very common: may affect more than 1 in 10 people
- Headache;
- Feeling dizzy or sick (nausea);
- Double vision (diplopia).

Common: may affect up to 1 in 10 people
- Short jerks of a muscle or group of muscles (myoclonic seizures);
- Difficulties in coordinating your movements or walking;
- Problems in keeping your balance, shaking (tremor), tingling (paresthesia) or muscle spasms, falling easily and getting bruises;
- Troubles with your memory, thinking or finding words, confusion;
- Rapid and uncontrollable movements of the eyes (nystagmus), blurred vision;
- A spinning sensation (vertigo), feeling drunk;
- Being sick (vomiting), dry mouth, constipation, indigestion, excessive gas in the stomach or bowel, diarrhoea;
- Decreased feeling or sensitivity, difficulty in articulating words, disturbance in attention;
- Noise in the ear such as buzzing, ringing or whistling;
- Irritability, trouble sleeping, depression;
- Sleepiness, tiredness or weakness (asthenia);
- Itching, rash.

Uncommon: may affect up to 1 in 100 people
- Slow heart rate, palpitations, irregular pulse or other changes in the electrical activity of your heart (conduction disorder);
- Exaggerated feeling of wellbeing, seeing and/or hearing things which are not there;
- Allergic reaction to medicine intake, hives;
- Blood tests may show abnormal liver function, liver injury;
- Thoughts of harming or killing yourself or attempting suicide: tell your doctor straight away;
- Feeling angry or agitated;
- Abnormal thinking or losing touch with reality;
- Serious allergic reaction which causes swelling of the face, throat, hands, feet, ankles, or lower legs;
- Fainting;
- Abnormal involuntary movements (dyskinesia).

Not known: frequency cannot be estimated from available data
- Abnormal rapid heartbeat (ventricular tachyarrhythmia);
- A sore throat, high temperature and getting more infections than usual. Blood tests may show a severe decrease in a specific class of white blood cells (agranulocytosis);
- A serious skin reaction which may include a high temperature and other flu-like symptoms, a rash on the face, extended rash, swollen glands (enlarged lymph nodes). Blood tests may show increased levels of liver enzymes and a type of white blood cell (eosinophilia);
- 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);
- Convulsion.

Additional side effects when given as an intravenous infusion
There may be local side effects.

Common: may affect up to 1 in 10 people
- Injection site pain or discomfort or irritation.

Uncommon: may affect up to 1 in 100 people
- Injection site redness.

Additional side effects in children

The additional side effects in children were fever (pyrexia), runny nose (nasopharyngitis), sore throat (pharyngitis), eating less than usual (decreased appetite), changes in behaviour, not acting like themselves (abnormal behavior) and lacking in energy (lethargy). Feeling sleepy (somnolence) is a very common side effect in children and may affect more than 1 in 10 children.

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 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 injections.

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.

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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: https://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.