SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trelema 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg lacosamide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Pink coloured, oval and biconvex f/c tablets, with a break-score on both sides and with a length of about 10.3 mm.

The tablet can be divided into equal doses.

Trelema 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.

Trelema 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.

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
*Children less than 50 kg should preferably start the treatment with Trelema 10 mg/ml syrup		

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 primarygeneralised 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 $\geq$ 6 mg/kg/day or $\geq$ 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 ($CL_{CR} \leq$ 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 (CLCR ≤ 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 generalised 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

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.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicinal products in several indications. A meta-analysis of randomised

placebo controlled clinical studies of anti-epileptic 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 trials 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 medicinal product (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 trials 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 trials. An *in vitro* study indicated that lacosamide is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

In vivo data

Lacosamide does not inhibit or induce CYP2C19 and 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 trials lacosamide did not significantly affect the plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and by valproic acid. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other anti-epileptic 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 trial there was no clinically relevant interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others

Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between lacosamide and metformin.

Co-administration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.

Although no pharmacokinetic data on the interaction of lacosamide with alcohol are available, a pharmacodynamic effect cannot be excluded.

Lacosamide has a low protein binding of less than 15%. Therefore, clinically relevant interactions with other medicinal products through competition for protein binding sites are considered unlikely.

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 anti-epileptic medicinal products, it has been shown that in the offspring of women treated with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy, however, the extent to which the treatment and/or the illness is responsible has not been elucidated.

Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to lacosamide

There are no adequate data from the use of lacosamide in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses (see section 5.3). The potential risk for humans is unknown.

Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breast-feeding

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.

Summary of safety profile

Based on the analysis of pooled placebo-controlled clinical trials in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9% of patients 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 trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions (≥ 10%) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6% for patients treated with lacosamide and 15.6% for patients treated with carbamazepine CR.

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

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic system 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[1] 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[3]
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			Liver function test	

System organ class	Very common	Common	Uncommon	Not known
disorders			abnormal[2] Hepatic enzyme increased (> 2 x ULN) [1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema[1] Urticaria[1]	Stevens-Johnson syndrome[1] Toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

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

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

Multi-organ hypersensitivity reactions

Multi-organ 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 multi-organ 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 ($\geq$ 1/10) compared to adult population ($\geq$ 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 ($\geq$ 65 years of age) appear to be similar to that observed in patients less than 65 years of age. However, a higher incidence ($\geq$ 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 Yellow Card Scheme,

Website: www.mhra.gov.uk/yellowcard,
or search for MHRA Yellow Card in the Google Play or Apple App Store.

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).

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 stabilisation of hyper-excitable 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, multi-centre, double-blind, randomised trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were 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 trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 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 clinical expression in children from 4 years of age and in adults. The efficacy of lacosamide in children aged 4 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 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 generalised tonic-clonic seizures)

The efficacy of lacosamide as adjunctive therapy in patients 4 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic seizures (PGTCS) was established in a 24-week double-blind, randomised, placebo-controlled, parallel-group, multi-center 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 randomised 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 treatedwith 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 patientsweighing 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 forthe 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. Trelema 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 trial with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations indicating that the importance of this pathway is minor. The plasma concentration of O-desmethyl-lacosamide is approximately 15% of the concentration of lacosamide in plasma. This major metabolite has no known pharmacological activity.

Elimination

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

urine and less than 0.5% in the 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 trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

Renal impairment
The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with 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 normalised 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 one

placebo-controlled randomised study and three open-label studies in 414 children with epilepsy aged 6 months to 17 years. The administered lacosamide doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, with a maximum of 600 mg/day for children weighing 50 kg or more.
The typical plasma clearance was estimated to be 1.04 L/h, 1.32 L/h and 1.86 L/h for children weighing 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.92 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 cardio-depressant 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 embryo-foetotoxic 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 - low substituted
Hydroxypropylcellulose
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Tablet coat
Poly(vinyl alcohol)
Macrogol
Titanium dioxide (E 171)
Talc
Red iron oxide (E 172)
Black iron oxide (E 172)
Indigo carmine aluminium lake (E 132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 14, 20, 28, 30, 40, 56, 60, 84, 90, 100, 112, 120 and 168 film-coated tablets in PVC/Al blister or PVC/PVdC/Al blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH
Schlossplatz
8502 Lannach
Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2023

10 DATE OF REVISION OF THE TEXT

23/04/2023