

To be sold by retail on the prescription of Neurologist Only

LACOSAM INJECTION

1. Generic Name:

Lacosamide Injection 10 mg/ml

2. Qualitative and quantitative composition:

Each ml contains: Lacosamide Ph. Eur. 10mg

Water for Injection IP q.s

Qualitative & Quantitative Formula

Sodium Chloride

Hydrochloric Acid

3. Dosage form and strength:

Dosage form: Injection

Strength: Lacosamide Injection 10 mg/ml

4. Clinical particulars:

4.1 Therapeutic indication:

As an adjunctive treatment of partial onset seizures in patients >17 years of age.

4.2 Posology and method of administration:

Lacosamide must be taken twice a day. Lacosamide can be initiated with either oral or intravenous administration. The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Depending on response and tolerability, the maintenance dose can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 400 mg (200 mg twice a day). In accordance with current clinical practice, if Lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Solution for infusion:

The solution for infusion is infused over a period of 30 to 60 minutes twice daily. Lacosamide solution for infusion can be administered i.v. without further dilution or may be mixed with diluents. Conversion to or from oral and i.v. administration can be done directly without titration. The total daily dose and twice daily administration should be maintained. There is experience with twice daily infusions of Lacosamide up to 5 days.

Special population

Renal impairment:

No dose adjustment is necessary in mildly and moderately renally impaired patients (CLCR > 30 ml/min). A maximum dose of 250 mg/day is recommended for patients with severe renal impairment (CLCR 30 ml/min) and in patients with end stage renal disease. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with

no known pharmacological activity). In all patients with renal impairment, the dose titration should be performed with caution.

Hepatic impairment

No dose adjustment is needed for patients with mild to moderate hepatic impairment. The dose titration in these patients should be performed with caution considering co-existing renal impairment. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients.

Elderly (over 65 years of age)

No dose reduction is necessary in elderly patients. The experience with lacosamide in elderly patients with epilepsy is limited. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly.

Paediatric population

Lacosamide is not recommended for use in children and adolescents below the age of 17 as safety and effectiveness have not been established in these age groups.

Compatibility and Stability

Lacosamide injection can be administered intravenously without further dilution or may be mixed with diluents. Lacosamide injection 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 polyvinyl chloride (PVC) bags at ambient room temperature 15-30°C (59-86°F).

Diluents:

Sodium Chloride Injection 0.9% (w/v)

Dextrose Injection 5% (w/v)

Lactated Ringer's Injection

The stability of Lacosamide injection in other infusion solutions has not been evaluated. Product with particulate matter or discoloration should not be used. Any unused portion of Lacosamide injection should be discarded.

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

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

4.4 Special warnings and precautions for use:

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should sign of suicidal ideation or behaviour emerge.

Cardiac rhythm and conduction

Dose-related prolongations in PR interval with lacosamide have been observed in clinical

studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. myocardial ischaemia/infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including anti arrhythmics and sodium channel blocking antiepileptic medicinal products, as well as in elderly patients.

In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

In the placebo-controlled 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.

4.5 Drug-Interaction:

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

In vitro data

Data generally suggest that lacosamide has a low interaction potential. In vitro studies indicate that the enzymes CYP1A2, 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 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 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.

4.6 Use in special populations

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. The potential risk for humans is unknown.

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

Breastfeeding

It is unknown whether lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. Animal studies have shown excretion of lacosamide in breast milk. For precautionary measures, breast-feeding should be discontinued during treatment with lacosamide.

Fertility

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

4.7 Effects on ability to drive and use machines:

Lacosamide has minor to moderate influence on the ability to drive and use machines. Lacosamide treatment has been associated with dizziness or blurred vision.

Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of lacosamide on their ability to perform such activities.

4.8 Undesirable effects:

Summary of safety profile

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

Tabulated list of adverse reactions

The table below shows the frequencies of adverse reactions which have been reported in clinical trials and post-marketing experience. The frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ 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	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 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		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 trials in epilepsy patients the incidence rate of reported first-degree AV Block is uncommon, 0.7 %, 0 %, 0.5 % and 0 % for lacosamide 200 mg, 400 mg, 600 mg or placebo, respectively. No second- or higher degree AV Block was seen in these studies.

However, cases with second- and third-degree AV Block associated with lacosamide treatment have been reported in post-marketing experience. In the monotherapy clinical trial comparing lacosamide to carbamazepine CR the extent of increase in PR interval was comparable between lacosamide and carbamazepine.

The incidence rate for syncope reported in pooled adjunctive therapy clinical trials is uncommon and did not differ between lacosamide (n=944) treated epilepsy patients (0.1 %) and placebo (n=364) treated epilepsy patients (0.3 %). In the monotherapy clinical trial comparing lacosamide to carbamazepine CR, syncope was reported in 7/444 (1.6 %) lacosamide patients and in 1/442 (0.2 %) carbamazepine CR patients.

Atrial fibrillation or flutter were not reported in short term clinical trials; however, both have been reported in open-label epilepsy trials and in post-marketing experience.

Laboratory abnormalities

Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic medicinal products. Elevations of ALT to $\geq 3x$ ULN occurred in 0.7 % (7/935) of Lacosam 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.

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 side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose:

Symptoms

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

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

Management

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

5. Pharmacological properties:

5.1 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 hyper excitable neuronal membranes.

5.2 Pharmacodynamic properties:

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

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 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.

5.3 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 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 radiolabelled 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. The exposure of the O-desmethyl metabolite was several-fold increase 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.

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 % increase 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.

6. Nonclinical properties:

In the toxicity studies, the plasma concentrations of lacosamide obtained were similar or only marginally higher than those observed in patients, which leaves low or non-existing margins to human exposure.

A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardio depressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing.

In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.

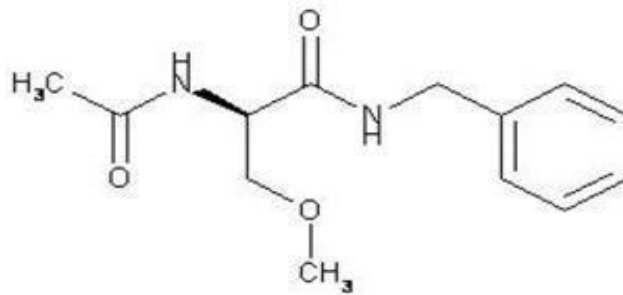
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.

In reproductive and developmental toxicity studies in rodents and rabbits, no teratogenic effects but an increase in numbers of stillborn pups and pup deaths in the peripartum period, and slightly reduced live litter sizes and pup body weights were observed at maternal toxic doses in rats corresponding to systemic exposure levels similar to the expected clinical exposure. Since higher exposure levels could not be tested in animals due to maternal toxicity, data are insufficient to fully characterize the embryofetotoxic and teratogenic potential of lacosamide.

Studies in rats revealed that lacosamide and/or its metabolites readily crossed the placental barrier.

7. Description:

The chemical name of lacosamide, the single (R)-enantiomer, is (R)-2-acetamido-N-benzyl-3-methoxypropionamide (IUPAC). Lacosamide is a functionalized amino acid. Its molecular formula is $C_{13}H_{18}N_2O_3$ and its molecular weight is 250.30. The chemical structure is:



Lacosamide is a white to light yellow powder. It is sparingly soluble in water and slightly soluble in acetonitrile and ethanol.

Diluents:

Sodium Chloride Injection 0.9% (w/v) Dextrose Injection 5% (w/v)

Lactated Ringer's Injection

Product with particulate matter or discoloration should not be used.

Product Description:

Clear colorless solution filled in 20ml (molded) USP Type I flint glass vial, stoppered with Grey rubber stopper, and sealed with green flip off seal.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned below:

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.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

Lacosamide injection is available as single dose vials of 20 ml.

8.4 Storage and handing instructions:

Store at a temperature not exceeding 30°C. Keep out of reach of children. Sterile single dose vial.

Discard unused portion. For I.V. infusion only.

Lacosamide injection can be administered intravenously without further dilution or may be mixed with diluents. Lacosamide injection 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 polyvinyl chloride (PVC) bags at ambient room temperature 15-30°C (59-86°F).

9. Patient Counselling Information

Package leaflet: Information for the user

Lacosam 10 mg/ml solution for infusion

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?

- What LACOSAM is and what it is used for

- What you need to know before you take LACOSAM
- How to take LACOSAM
- Possible side effects
- How to store LACOSAM
- Contents of the pack and other information

9.1 What LACOSAM is and what it is used for

What Lacosam is

Lacosam 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 Lacosam is used for

- Lacosam is used in adults.
- It is used 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 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).

9.2 What you need to know before you take LACOSAM

Do not use LACOSAM:

- if you are allergic to lacosamide, or any of the other ingredients of this medicine. 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 Lacosam 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 or pharmacist before taking LACOSAM 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 particularly 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. Lacosam 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 Lacosam.

If you are taking Lacosam, talk to your doctor if you are experiencing a new type of seizure or worsening of existing seizures.

If you are taking Lacosam 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.

Children under 4 years

Lacosam is not recommended for children aged under 4 years. 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 Lacosam

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 Lacosam 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 Lacosam.

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 Lacosam on your body:

- medicines for fungal infections called fluconazole, itraconazole or ketoconazole;
- a medicine for HIV called ritonavir;
- medicines for bacterial infections called 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 Lacosam.

Lacosam with alcohol

As a safety precaution do not use Lacosam with alcohol.

Pregnancy and breast-feeding

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

It is not recommended to use Lacosam if you are pregnant or breast feeding, as the effects of Lacosam on pregnancy and the unborn baby or the new-born child are not known. Also, it is not known whether Lacosam 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 Lacosam 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 Lacosam may make you feel dizzy or cause blurred vision.

Lacosam contains sodium

This medicine contains 2.6 mmol (or 59.8 mg) of sodium in each vial. You need to know this if you are on a controlled sodium diet.

9.3 How to take LACOSAM

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 Lacosam

- Lacosam 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 Lacosam for up to 5 days. For longer term treatment Lacosam 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 Lacosam twice each day – once in the morning and once in the evening.
- Try to use it at about the same time each day.

How much to use

Listed below are the normal recommended doses of Lacosam 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 Lacosam on its own

The usual starting dose of Lacosam is 50 mg twice a day.

The treatment with Lacosam may also start with a dose of 100 mg of Lacosam 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.

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

When you use Lacosam with other antiepileptic medicines The usual starting dose of Lacosam 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 Lacosam treatment with a single “loading” dose of 200 mg. You would then start your ongoing maintenance dose 12 hours later.

When you use Lacosam with other antiepileptic medicines

Your doctor will decide the dose of Lacosam based on your body weight.

If you stop using Lacosam

If your doctor decides to stop your treatment with Lacosam, 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.

9.4 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.

Not known: frequency cannot be estimated from available data

- 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

Common: may affect up to 1 in 10 children

- Runny nose (nasopharyngitis);
- Fever (pyrexia);
- Sore throat (pharyngitis);
- Eating less than usual.

Uncommon: may affect up to 1 in 100 children

- Feeling sleepy or lacking in energy (lethargy).

Not known: frequency cannot be estimated from available data

- Changes in behaviour, not acting like themselves.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store LACOSAM

- 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 Lacosam 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.

9.6 Contents of the pack and other information

What Lacosam contains

- The active substance is lacosamide.
- 1 ml Lacosam solution for infusion contains 10 mg lacosamide.
- 1 vial contains 20 ml Lacosam solution for infusion equivalent to 200 mg lacosamide.
- The other ingredients are: sodium chloride, hydrochloric acid, water for injections.

What Lacosam looks like and contents of the pack

- Lacosam 10 mg/ml solution for infusion is a clear, colourless solution.
- Lacosam 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.

The following information is intended for medical or healthcare professionals only.

Each vial of Lacosam solution for infusion must be used only once (single use). Any unused solution should be discarded.

Lacosam 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.

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.
 Inrad -382 721, Dist. Mehsana, INDIA
 At – J-174, J-168, J-168/1
 MIDC, Tarapur, Dist.
 Thane- 401506

Or

Manufactured by:
 Torrent Pharmaceuticals Ltd.
 Inrad -382 721, Dist. Mehsana, INDIA
 At: 2,3,4 & 5, Sec-6 B, IIE, SIDCUL,
 Ranipur, Haridwar-249 403

11. Details of permission or licence number with date

Mfg Lic No.: KD/2035 A issued date 15.12.2018

Mfg Lic No.:5/UA/LL/SC/P-2016 issued on 19.10.2020

12. Date of revision

MAR 2021

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/LACOSAM INJECTION 10mg/ml/MAR-21/05/PI