For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LACOSAM

1. Generic Name

Lacosamide Tablets Ph. Eur

2. Qualitative & Quantitative composition

LACOSAM 50

Each film coated tablet contains:

Lacosamide Ph. Eur. ….50mg

Colours: Titanium Dioxide I.P. and Red Oxide of Iron

LACOSAM 100

Each film coated tablet contains:

Lacosamide Ph. Eur. ….100mg

Colours: Titanium Dioxide I.P. and Yellow Oxide of Iron

LACOSAM 150

Each film coated tablet contains:

Lacosamide Ph. Eur. ….150mg

Colours: Titanium Dioxide I.P. and Lake of Sunset Yellow

LACOSAM 200

Each film coated tablet contains:

Lacosamide Ph. Eur. ….200mg

Colour: Titanium Dioxide I.P.

Excipients used are as below:

LACOSAM 50:

MICROCRYSTALLINE CELLULOSE,

Crospovidone

Hydroxypropylcellulose

COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
POLYETHYLENE GLYCOL
RED OXIDE OF IRON,
TITANIUM DIOXIDE,
Talc

LACOSAM 100:

MICROCRYSTALLINE CELLULOSE,
Crospovidone
Hydroxypropylcellulose
COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
POLYETHYLENE GLYCOL
YELLOW OXIDE OF IRON,
TITANIUM DIOXIDE,
Talc

LACOSAM 150:

MICROCRYSTALLINE CELLULOSE,
Crospovidone
Hydroxypropylcellulose
COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
polyethylene glycol
LAKE OF SUNSET YELLOW,
TITANIUM DIOXIDE,
Talc

LACOSAM 200:

MICROCRYSTALLINE CELLULOSE,

Crospovidone

Hydroxypropylcellulose

COLLOIDAL SILICON DIOXIDE

LOW-SUB.HYDROXYPROPYL CELLULOSE,

MAGNESIUM STEARATE,

HYDROXY PROPYL METHYL CELLULOSE

polyethylene glycol

TITANIUM DIOXIDE,

Talc

3. DOSAGE FORM AND STRENGTH

DOSAGE FORM Film coated tablet

STRENGTH: 50 mg, 100 mg, 150 mg & 200 mg

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

Posology

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

Monotherapy

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

Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).

In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy

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

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

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

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

Initiation of Lacosamide treatment with a loading dose

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

Discontinuation

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

Special populations

Elderly (over 65 years of age)

No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients. There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day.
Renal impairment

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

disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment

A maximum dose of 300 mg/day is recommended for patients with mild to moderate hepatic impairment.

The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been

evaluated in severely hepatic impaired patients. Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population

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

Method of administration

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

4.3 Contraindications

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

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. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.

In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state. Second degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy trials and in post-marketing experience.

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

Dizziness

Treatment with lacosamide has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise

caution until they are familiar with the potential effects of the medicine.

4.5 Drugs Interactions

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 (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

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

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).

4.8 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 (≥ 10 %) for lacosamide were headache and dizziness. The discontinuation rate due to adverse reactions was 10.6 % for patients treated with lacosamide and 15.6 % for patients treated with carbamazepine CR.

Tabulated list of adverse reactions

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

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

			Psychotic disorder [1] Suicide attempt [1] Suicidal ideation Hallucination [1]	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2]	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]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth		

		Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal [2] Hepatic enzyme increased (> 2x ULN) [1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema [1] Urticaria[1]	Stevens-Johnson syndrome [1] Toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[1] Adverse reactions reported in post marketing experience.

[2] See Description of selected adverse reactions.

[3] Reported in open-label 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 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 ≥ 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.

Paediatric population

The safety profile of lacosamide in placebo-controlled and in open-label studies (n=408) in adjunctive therapy in children from 4 years of age was consistent with the safety profile observed in adults although the frequency of some adverse reactions (somnolence, vomiting and convulsion) was increased and additional adverse reactions (nasopharyngitis, pyrexia, pharyngitis, decreased appetite, lethargy and abnormal behaviour) have been reported in paediatric patients: nasopharyngitis (15.7 %), vomiting (14.7 %), somnolence (14.0 %), dizziness (13.5 %), pyrexia (13.0 %), convulsion (7.8 %), decreased appetite (5.9 %), pharyngitis (4.7 %), lethargy (2.7 %) and abnormal behaviour (1.7 %).

A total of 67.8 % of patients randomised to lacosamide and 58.1 % of patients randomised to placebo reported at least 1 adverse reaction.

Behavioural, cognition and emotional functioning were measured by the questionnaires Achenbach CBCL and BRIEF that were applied at baseline and throughout the studies and where mainly stable during the course of the trials.

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.

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**.**

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 and safety has been demonstrated.

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.

5.3 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. Lacosam 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 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.

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).

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

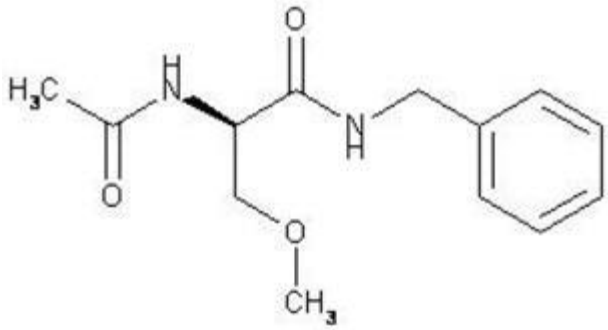
In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol 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 C13H18N2O3 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.

Product Description:

LACOSAM 50:

Light pink coloured, round shaped, biconvex, film coated tablets, plain on both sides.

LACOSAM 100:

Light Yellow coloured, round shaped, biconvex, film coated tablets with breakline on one side and plain on other side.

LACOSAM 150:

Light orange coloured, round shaped, biconvex, film coated tablets with breakline on one side and plain on other side.

LACOSAM 200:

White to off white, round shaped, biconvex, film coated tablets with breakline on one side and plain on other side.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than expiry date.

8.3 Packaging information

Lacosam 50, Lacosam 100, Lacosam 150 & Lacosam 200 are available in blister of 10 tablets.

8.4 Storage and Handing Instructions

Lacosam 50

Store at a temperature not exceeding 30°C, Protected from moisture.

Lacosam 100, 150 & 200

Store at a temperature not exceeding 30°C. Protected from moisture.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the patient

Lacosam 50 mg film-coated tablets

Lacosam 100 mg film-coated tablets

Lacosam 150 mg film-coated tablets

Lacosam 200 mg film-coated tablets

lacosamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet

1. What Lacosam is and what it is used for

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

2. What you need to know before you take Lacosam

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

Warnings and precautions

Talk to your doctor before taking 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 particulary slow, fast or irregular heart beat (such as AV block, atrial fibrillation and atrial flutter).
- you have severe heart disease such as heart failure or have had a heart attack.
- you are often dizzy or fall over. 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 taking Lacosam.

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 taking 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 used to treat bacterial infections called clarithromycin or rifampicin;

- an herbal medicine used to treat mild anxiety and depression called St. John's wort.

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

Lacosam with alcohol

As a safety precaution do not take Lacosam with alcohol.

Pregnancy and breast-feeding

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

It is not recommended to take 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 take 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.

3. How to take Lacosam

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

Taking Lacosam

- Take Lacosam twice each day - once in the morning and once in the evening.
- Try to take it at about the same time each day.
- Swallow the Lacosam tablet with a glass of water.
- You may take Lacosam with or without food.

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

How much to take

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 take Lacosam on its own

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

Your doctor may also prescribe a starting 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 between 100 mg and 300 mg twice a day.

When you take 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 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.

Children and adolescent weighing less than 50 kg

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

If you take more Lacosam than you should

If you have taken more Lacosam than you should, contact your doctor immediately. Do not try to drive.

You may experience:

- dizziness;
- feeling sick (nausea) or being sick (vomiting);
- fits (seizures), heart beat problems such a slow, fast or irregular heartbeat, coma or a fall in blood pressure with rapid heartbeat and sweating.

If you forget to take Lacosam

- If you have missed a dose within the first 6 hours of the scheduled dose, take it as soon as you remember.
- If you have missed a dose beyond the first 6 hours of the scheduled dose, do not take the missed tablet anymore. Instead take Lacosam at the next time that you would normally take it.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Lacosam

- Do not stop taking Lacosam without talking to your doctor, as your epilepsy may come back again or become worse.
- If your doctor decides to stop your treatment with Lacosam, they will tell you how to decrease the dose step by step.

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

4. Possible side effects

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

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

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

Very common: may affect more than 1 in 10 people

- Headache;
- Feeling dizzy or sick (nausea);
- Double vision (diplopia).

Common: may affect up to 1 in 10 people

- Problems in keeping your balance, difficulties in coordinating your movements or walking, 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 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.

5. How to store Lacosam

Lacosam 50

Store at a temperature not exceeding 30°C, Protected from moisture.

Lacosam 100, 150 & 200

Store at a temperature not exceeding 30°C. Protected from moisture.

Keep out of reach of children.

6. Contents of the pack and other information

Lacosam 50, Lacosam 100, Lacosam 150 & Lacosam 200 are available in blister of 10 tablets.

What Lacosam contains

- The active substance is lacosamide.

One tablet of Lacosam 50 mg contains 50 mg lacosamide.

One tablet of Lacosam 100 mg contains 100 mg lacosamide.

One tablet of Lacosam 150 mg contains 150 mg lacosamide.

One tablet of Lacosam 200 mg contains 200 mg lacosamide.

Other ingredients are:

LACOSAM 50:

MICROCRYSTALLINE CELLULOSE,

Crospovidone

Hydroxypropylcellulose
COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
POLYETHYLENE GLYCOL
RED OXIDE OF IRON,
TITANIUM DIOXIDE,
Talc
LACOSAM 100:
MICROCRYSTALLINE CELLULOSE,
Crospovidone
Hydroxypropylcellulose
COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
POLYETHYLENE GLYCOL
YELLOW OXIDE OF IRON,
TITANIUM DIOXIDE,
Talc
LACOSAM 150:
MICROCRYSTALLINE CELLULOSE,
Crospovidone
Hydroxypropylcellulose
COLLOIDAL SILICON DIOXIDE
LOW-SUB.HYDROXYPROPYL CELLULOSE,
MAGNESIUM STEARATE,
HYDROXY PROPYL METHYL CELLULOSE
POLYETHYLENE GLYCOL
LAKE OF SUNSET YELLOW,
TITANIUM DIOXIDE,
Talc

LACOSAM 200:

MICROCRYSTALLINE CELLULOSE,

Crospovidone

Hydroxypropylcellulose

COLLOIDAL SILICON DIOXIDE

LOW-SUB.HYDROXYPROPYL CELLULOSE,

MAGNESIUM STEARATE,

HYDROXY PROPYL METHYL CELLULOSE

POLY ETHYLENE GLYCOL

TITANIUM DIOXIDE,

Talc

10. DETAILS OF MANUFACTURER

LACOSAM 50:

Manufactured By:

Ravenbhel Biotech

EPIP, SIDCO, Kartholi,

Bari-Brahmana, Jammu-181133

LACOSAM 100 & 200:

TORRENT PHARMACEUTICALS LTD

32 No., Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135.

LACOSAM 150:

TORRENT PHARMACEUTICALS LTD.

Vill. Bhud & Makhnu Majra,

The. Baddi-173 205, Dist. Solan (H.P.), INDIA**.**

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

LACOSAM 50: JK/01/11-12/192 issued on 04.09.2015

LACOSAM 100 & 200: Mfg Lic No.: M/563/2010 issued on 24.07.2018

LACOSAM 150: Mfg Lic No.: MNB/05/183 issued on 25.07.2018

12. DATE OF REVISION

July -2019

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/LACOSAM 50,100,150,200mg/JUL-19/04/PI