

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Lacosamide Accord 50 mg film-coated tablets

One film-coated tablet contains 50 mg lacosamide.

### Lacosamide Accord 100 mg film-coated tablets

One film-coated tablet contains 100 mg lacosamide.

### Lacosamide Accord 150 mg film-coated tablets

One film-coated tablet contains 150 mg lacosamide.

### Lacosamide Accord 200 mg film-coated tablets

One film-coated tablet contains 200 mg lacosamide.

### Excipient(s) with known effect:

50 mg: Each film-coated tablet contains 0.105 mg of lecithin (soya)  
100 mg: Each film-coated tablet contains 0.210 mg of lecithin (soya)  
150 mg: Each film-coated tablet contains 0.315 mg of lecithin (soya)  
200 mg: Each film-coated tablet contains 0.420 mg of lecithin (soya)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

### Lacosamide Accord 50 mg film-coated tablets

Pink, oval, approximately 10.3 x 4.8 mm, coated tablets, debossed "L" on one side and "50" on other side.

### Lacosamide Accord 100 mg film-coated tablets

Dark yellow, oval, approximately 13.0 x 6.0 mm, coated tablets, debossed "L" on one side and "100" on other side.

### Lacosamide Accord 150 mg film-coated tablets

Salmon, oval, approximately 15.0 x 6.9 mm, coated tablets, debossed "L" on one side and "150" on other side.

### Lacosamide Accord 200 mg film-coated tablets

Blue, oval, approximately 16.4 x 7.6 mm, coated tablets, debossed “L” on one side and “200” on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Lacosamide Accord is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

### 4.2 Posology and method of administration

#### Posology

Lacosamide must be taken twice a day (usually once in the morning and once in the evening).

Lacosamide may be taken with or without food.

If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of lacosamide at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of lacosamide at the regularly scheduled time. Patients should not take a double dose.

#### Adolescents and children weighing 50 kg or more, and adults

The following table summarises the recommended posology for adolescents and children weighing 50 kg or more, and for adults. More details are provided in the table below.

	Monotherapy	Adjunctive therapy
Starting dose	100 mg/day or 200 mg/day	100 mg/day
Single loading dose (if applicable)	200 mg	200 mg
Titration (incremental steps)	50 mg twice a day (100 mg/day) at weekly intervals	50 mg twice a day (100 mg/day) at weekly intervals
Maximum recommended dose	up to 600 mg/day	up to 400 mg/day

#### *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 daily dose of 300 mg twice a day (600 mg/day).

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

#### *Adjunctive therapy*

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

### *Discontinuation*

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

### Special populations

#### *Elderly (over 65 years of age)*

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

#### *Renal impairment*

No dose adjustment is necessary in mildly and moderately renally impaired adult and paediatric patients ( $CL_{CR} > 30$  ml/min). In paediatric patients weighing 50 kg or more and in adult patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration ( $> 200$  mg daily) should be performed with caution.

In paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment ( $CL_{CR} \leq 30$  ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. In paediatric patients weighing less than 50 kg with severe renal impairment ( $CL_{CR} \leq 30$  ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all patients requiring haemodialysis a supplement of up to 50 % of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

#### *Hepatic impairment*

A maximum dose of 300 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.

The dose titration in these patients should be performed with caution considering co-existing renal impairment. In adolescents and adults weighing 50 kg or more, a loading dose of 200 mg may be considered, but further dose titration ( $> 200$  mg daily) should be performed with caution. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

#### *Paediatric population*

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

#### Adolescents and children weighing 50 kg or more

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

Children (from 4 years of age) and adolescents weighing less than 50 kg

The dose is determined based on body weight. It is therefore recommended to initiate treatment with the syrup and switch to tablets, if desired.

*Monotherapy*

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

Depending on response and tolerability, the maintenance dose can be further increased by 2 mg/kg/day every week. The dose should be gradually increased until the optimum response is obtained. In children weighing less than 40 kg, a maximum dose of up to 12 mg/kg/day is recommended. In children weighing from 40 to under 50 kg, a maximum dose of 10 mg/kg/day is recommended.

The following table summarises the recommended posology in monotherapy for children and adolescents weighing less than 50 kg.

Starting dose	2 mg/kg/day
Single loading dose	Not recommended
Titration (incremental steps)	2 mg/kg/day every week
Maximum recommended dose in patients < 40 kg	up to 12 mg/kg/day
Maximum recommended dose in patients ≥ 40 kg to < 50 kg	up to 10 mg/kg/day

*Adjunctive therapy*

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

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

The following table summarises the recommended posology in adjunctive therapy for children and adolescents weighing less than 50 kg.

Starting dose	2 mg/kg/day
Single loading dose	Not recommended
Titration (incremental steps)	2 mg/kg/day every week
Maximum recommended dose in patients < 20 kg	up to 12 mg/kg/day
Maximum recommended dose in patients ≥ 20 kg to < 30 kg	up to 10 mg/kg/day
Maximum recommended dose in patients ≥ 30 kg to < 50 kg	up to 8 mg/kg/day

*Loading dose*

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

Children less than 4 years

The safety and efficacy of lacosamide in children aged below 4 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, soya lecithin or to any of the excipients listed in section 6.1.

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

### **4.4 Special warnings and precautions for use**

#### Suicidal ideation and behaviour

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

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

#### Cardiac rhythm and conduction

Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.

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

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

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

#### Dizziness

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

#### Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

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

#### Excipients

Lacosamide Accord contains soya lecithin. Therefore, this medicinal product should be used with caution in patients allergic to peanut or soya.

#### 4.5 Interaction with other medicinal products and other forms of interaction

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

##### In vitro data

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

##### In vivo data

Lacosamide does not inhibit or induce CYP2C19 and 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 %.

##### 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 Fertility, pregnancy and lactation**

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

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

###### *Risk related to lacosamide*

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

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

##### Breastfeeding

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 randomized to lacosamide and 35.2 % of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions ( $\geq 10$  %) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and



gastrointestinal (GI) adverse reactions usually decreased over time.

In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomized to lacosamide and 1.6 % for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.

Incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions ( $\geq 10\%$ ) 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 <sup>(1)</sup>
Immune system disorders			Drug hypersensitivity <sup>(1)</sup>	Drug reaction with eosinophilia and systemic symptoms (DRESS) <sup>(1,2)</sup>
Psychiatric disorders		Depression Confusional state Insomnia <sup>(1)</sup>	Aggression Agitation <sup>(1)</sup> Euphoric mood <sup>(1)</sup> Psychotic disorder <sup>(1)</sup> Suicide attempt <sup>(1)</sup> Suicidal ideation Hallucination <sup>(1)</sup>	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope <sup>(2)</sup>	Convulsion <sup>(3)</sup>
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block <sup>(1,2)</sup> Bradycardia <sup>(1,2)</sup> Atrial Fibrillation <sup>(1,2)</sup>	

			Atrial Flutter <sup>(1,2)</sup>	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal <sup>(2)</sup> Hepatic enzyme increased ( $> 2x$ ULN) <sup>(1)</sup>	
Skin and subcutaneous tissue disorders		Pruritus Rash <sup>(1)</sup>	Angioedema <sup>(1)</sup> Urticaria <sup>(1)</sup>	Stevens-Johnson syndrome <sup>(1)</sup> Toxic epidermal necrolysis <sup>(1)</sup>
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		

<sup>(1)</sup> Adverse reactions reported in post marketing experience.

<sup>(2)</sup> See Description of selected adverse reactions.

<sup>(3)</sup> 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  $\geq 3x$  ULN occurred in 0.7 % (7/935) of Lacosamide 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 open-label studies in adjunctive therapy in children from 4 years to less than 16 years was consistent with the safety profile observed in adults. In the paediatric population the most frequently reported adverse reactions were vomiting (17.1 %), dizziness (16.7 %), somnolence (12.1 %), headache (11.7 %) and convulsion (10.1 %). Additional adverse reactions reported in children were decreased appetite (6.6 %), lethargy (4.3 %) and abnormal behaviour (1.9 %).

#### Elderly population

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

#### Reporting of suspected adverse reactions

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

### **4.9 Overdose**

#### Symptoms

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

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

#### Management

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

## **5. PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

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

### Mechanism of action

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

The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

### Pharmacodynamic effects

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

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

### Clinical efficacy and safety

#### 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 randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 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, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

##### *Adjunctive therapy*

The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive

therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1,308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptic medicinal products in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23 %, 34 %, and 40 % for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

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

### Paediatric population

Partial-onset seizures have a similar clinical expression in children from 4 years of age and in adults. The efficacy of lacosamide in children aged 4 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).

## **5.2 Pharmacokinetic properties**

### Absorption

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

### Distribution

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

### Biotransformation

95 % of the dose is excreted in the urine as lacosamide and metabolites. The metabolism of lacosamide has not been completely characterised.

The major compounds excreted in urine are unchanged lacosamide (approximately 40 % of the dose) and its O-desmethyl metabolite less than 30 %.

A polar fraction proposed to be serine derivatives accounted for approximately 20 % in urine, but was detected only in small amounts (0-2 %) in human plasma of some subjects. Small amounts (0.5-2 %) of additional metabolites were found in the urine.

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

### Elimination

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

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

### Pharmacokinetics in special patient groups

#### *Gender*

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

#### *Renal impairment*

The AUC of lacosamide was increased by approximately 30% in mildly and moderately and 60% in severely renal impaired patients and patients with end-stage renal disease requiring haemodialysis compared to healthy subjects, whereas  $C_{max}$  was unaffected.

Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50 %. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). The exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

#### *Hepatic impairment*

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

#### *Elderly (over 65 years of age)*

In a study in elderly men and women including 4 patients > 75 years of age, AUC was about 30 and 50 % increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23 %, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.

A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

#### *Paediatric population*

The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in two open-label studies in 79 children with epilepsy aged 6 months to 17 years. The administered lacosamide doses ranged from 2 to 12 mg/kg/day (irrespective of the weight band of the child) in twice daily intake, with a maximum of 400 mg/day for children weighing 50 kg or more.

The typical plasma clearance was 1.08 L/h, 1.40 L/h and 1.92 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 adult patients (70 kg body weight).

### 5.3 Preclinical safety data

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

A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.

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

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Lacosamide Accord 50 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

##### Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Iron oxide red (E172)  
Iron oxide black (E172)  
Indigo carmine aluminum lake (E132)  
Lecithin (soya)

#### Lacosamide Accord 100 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Lecithin (soya)  
Iron oxide yellow (E172)

Lacosamide Accord 150 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Lecithin (soya)  
Iron oxide red (E172)  
Iron oxide black (E172)  
Iron oxide yellow (E172)

Lacosamide Accord 200 mg film-coated tablets

Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc



Titanium dioxide (E171)  
Lecithin (soya)  
Indigo carmine aluminum lake (E132)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Lacosamide Accord film-coated tablets are packed in PVC-PVDC/Aluminium blisters.  
Packs of 14, 56, 60 or 168 tablets  
Packs of 14 x 1 or 56 x 1 tablet in perforated unit dose blisters

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

## **7. MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom.

## **8. MARKETING AUTHORISATION NUMBER(S)**

Lacosamide Accord 50 mg film coated tablets:

EU/1/17/1230/001-004

EU/1/17/1230/017-018

Lacosamide Accord 100 mg film coated tablets:

EU/1/17/1230/005-008

EU/1/17/1230/019-020

Lacosamide Accord 150 mg film coated tablets:

EU/1/17/1230/009-012

EU/1/17/1230/021-022

Lacosamide Accord 200 mg film coated tablets:

EU/1/17/1230/013-016

EU/1/17/1230/023-024

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18 September 2017

**10. DATE OF REVISION OF THE TEXT**

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

## 1. NAME OF THE MEDICINAL PRODUCT

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

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lacosamide Accord 50 mg film-coated tablets

One film-coated tablet contains 50 mg lacosamide.

Lacosamide Accord 100 mg film-coated tablets

One film-coated tablet contains 100 mg lacosamide.

Lacosamide Accord 150 mg film-coated tablets

One film-coated tablet contains 150 mg lacosamide.

Lacosamide Accord 200 mg film-coated tablets

One film-coated tablet contains 200 mg lacosamide.

Excipient(s) with known effect:

50 mg: Each film-coated tablet contains 0.105 mg of lecithin (soya)  
100 mg: Each film-coated tablet contains 0.210 mg of lecithin (soya)  
150 mg: Each film-coated tablet contains 0.315 mg of lecithin (soya)  
200 mg: Each film-coated tablet contains 0.420 mg of lecithin (soya)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

Lacosamide Accord 50 mg film-coated tablets

Pink, oval, approximately 10.3 x 4.8 mm, coated tablets, debossed “L” on one side and “50” on other side.

Lacosamide Accord 100 mg film-coated tablets

Dark yellow, oval, approximately 13.0 x 6.0 mm, coated tablets, debossed “L” on one side and “100” on other side.

Lacosamide Accord 150 mg film-coated tablets

Salmon, oval, approximately 15.0 x 6.9 mm, coated tablets, debossed “L” on one side and “150” on other side.

Lacosamide Accord 200 mg film-coated tablets

Blue, oval, approximately 16.4 x 7.6 mm, coated tablets, debossed “L” on one side and “200” on other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Lacosamide Accord is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adolescents and children from 4 years of age weighing 50 kg or more and in adults with epilepsy.

### **4.2 Posology and method of administration**

#### Posology

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

If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of lacosamide at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of lacosamide at the regularly scheduled time. Patients should not take a double dose.

#### Adolescents and children weighing 50 kg or more, and adults

##### *Monotherapy*

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 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 medicinal product, 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).

Lacosamide Accord treatment initiation pack contains 4 different packages (one for each tablet strength) with 14 tablets each, for the first 2 to 4 weeks of therapy depending on the patient's response and tolerability. The packages are marked with ‘week 1 (2, 3 or 4)’.

On the first day of treatment the patient starts with Lacosamide Accord 50 mg tablets twice a day.

During the second week, the patient takes Lacosamide Accord 100 mg tablets twice a day.

Depending on response and tolerability, Lacosamide Accord 150 mg tablets may be taken twice a day during the third week and Lacosamide Accord 200 mg tablets twice a day during the fourth week.

##### *Discontinuation*

In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended

this be done gradually (e.g. taper the daily dose by 200 mg/week).

### Special populations

#### *Elderly (over 65 years of age)*

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

#### *Renal impairment*

No dose adjustment is necessary in mildly and moderately renally impaired adult and paediatric patients ( $CL_{CR} > 30$  ml/min). A maximum dose of 250 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with severe renal impairment ( $CL_{CR} \leq 30$  ml/min) or with end-stage renal disease. In paediatric patients weighing less than 50 kg with severe renal impairment ( $CL_{CR} \leq 30$  ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all patients requiring haemodialysis a supplement of up to 50 % of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity). In all patients with renal impairment, the dose titration should be performed with caution (see section 5.2).

#### *Hepatic impairment*

A maximum dose of 300 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment.

The dose titration in these patients should be performed with caution considering co-existing renal impairment. Based on data in adults, in paediatric patients weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2). Lacosamide should be administered to adult and paediatric patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

#### *Paediatric population*

##### Adolescents and children weighing 50 kg or more

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

##### Children (from 4 years of age) and adolescents weighing below 50 kg

This presentation is not suitable for this category of patients.

##### Children less than 4 years

The safety and efficacy of lacosamide in children aged below 4 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, soya lecithin or to any of the excipients listed in section 6.1.

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

## 4.4 Special warnings and precautions for use

### Suicidal ideation and behaviour

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

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

### Cardiac rhythm and conduction

Dose-related prolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems, severe cardiac disease (e.g. history of myocardial infarction or heart failure), in elderly patients, or when lacosamide is used in combination with products known to be associated with PR prolongation.

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

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

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

### Dizziness

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

### Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

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

### Excipients

Lacosamide Accord contains soya lecithin. Therefore, this medicinal product should be used with caution in patients allergic to peanut or soya.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

### In vitro data

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

#### In vivo data

Lacosamide does not inhibit or induce CYP2C19 and 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 %.

#### 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 Fertility, pregnancy and lactation**

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

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

#### *Risk related to lacosamide*

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

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

#### Breastfeeding

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 randomized to lacosamide and 35.2 % of patients randomized to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions ( $\geq 10$  %) with lacosamide treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose-related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.

In all of these controlled studies, the discontinuation rate due to adverse reactions was 12.2 % for patients randomized to lacosamide and 1.6 % for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of lacosamide therapy was dizziness.

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most frequently reported adverse reactions ( $\geq 10$  %) 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 <sup>(1)</sup>
Immune system disorders			Drug hypersensitivity <sup>(1)</sup>	Drug reaction with eosinophilia and systemic symptoms (DRESS) <sup>(1,2)</sup>
Psychiatric disorders		Depression Confusional state Insomnia <sup>(1)</sup>	Aggression Agitation <sup>(1)</sup> Euphoric mood <sup>(1)</sup> Psychotic disorder <sup>(1)</sup> Suicide attempt <sup>(1)</sup> Suicidal ideation Hallucination <sup>(1)</sup>	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope <sup>(2)</sup>	Convulsion <sup>(3)</sup>
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block <sup>(1,2)</sup> Bradycardia <sup>(1,2)</sup> Atrial Fibrillation <sup>(1,2)</sup> Atrial Flutter <sup>(1,2)</sup>	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal <sup>(2)</sup> Hepatic enzyme increased	

			(> 2x ULN) <sup>(1)</sup>	
Skin and subcutaneous tissue disorders		Pruritus Rash <sup>(1)</sup>	Angioedema <sup>(1)</sup> Urticaria <sup>(1)</sup>	Stevens-Johnson syndrome <sup>(1)</sup> Toxic epidermal necrolysis <sup>(1)</sup>
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		

<sup>(1)</sup> Adverse reactions reported in post marketing experience.

<sup>(2)</sup> See Description of selected adverse reactions.

<sup>(3)</sup> 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  $\geq 3x$  ULN occurred in 0.7 % (7/935) of Lacosamide 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 open-label studies in adjunctive therapy in children from 4 years to less than 16 years was consistent with the safety profile observed in adults. In the paediatric population the most frequently reported adverse reactions were vomiting (17.1 %), dizziness (16.7 %), somnolence (12.1 %), headache (11.7 %) and convulsion (10.1 %). Additional adverse reactions reported in children were decreased appetite (6.6 %), lethargy (4.3 %) and abnormal behaviour (1.9 %).

#### Elderly population

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

#### Reporting of suspected adverse reactions

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

### **4.9 Overdose**

#### Symptoms

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

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

#### Management

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

#### Mechanism of action

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

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

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

#### Pharmacodynamic effects

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

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

#### Clinical efficacy and safety

##### 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 randomized to carbamazepine CR or lacosamide, provided as tablets, in a 1:1 ratio. The dose was based on dose-response and ranged from 400 to 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, randomized trial. In this study, 425 patients aged 16 to 70 years with uncontrolled partial-onset seizures taking stable doses of 1 or 2 marketed antiepileptic medicinal products were randomized to be converted to lacosamide monotherapy (either 400mg/day or 300mg/day in a 3:1 ratio). In treated patients who completed titration and started withdrawing antiepileptic medicinal products (284 and 99 respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

##### *Adjunctive therapy*

The efficacy of lacosamide as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicenter, randomized, placebo-controlled clinical trials with a 12-week maintenance period. Lacosamide 600 mg/day was also shown to be effective in controlled adjunctive therapy trials, although the efficacy was similar to 400 mg/day and patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse reactions. Thus, the 600 mg/day dose is not recommended. The maximum recommended dose is 400 mg/day. These trials, involving 1,308 patients with a history of an average of 23 years of partial-onset seizures, were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with 1-3 antiepileptic

medicinal products in patients with uncontrolled partial-onset seizures with or without secondary generalisation. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23 %, 34 %, and 40 % for placebo, lacosamide 200 mg/day and lacosamide 400 mg/day.

### Paediatric population

Partial-onset seizures have a similar clinical expression in children from 4 years of age and in adults. The efficacy of lacosamide in children aged 4 years and older has been extrapolated from data of adolescents and adults with partial-onset seizures, for whom a similar response was expected provided the paediatric dose adaptations are established (see section 4.2) and safety has been demonstrated (see section 4.8).

## **5.2 Pharmacokinetic properties**

### Absorption

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

### Distribution

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

### Biotransformation

95 % of the dose is excreted in the urine as lacosamide and metabolites. The metabolism of lacosamide has not been completely characterised.

The major compounds excreted in urine are unchanged lacosamide (approximately 40 % of the dose) and its O-desmethyl metabolite less than 30 %.

A polar fraction proposed to be serine derivatives accounted for approximately 20 % in urine, but was detected only in small amounts (0-2 %) in human plasma of some subjects. Small amounts (0.5-2 %) of additional metabolites were found in the urine.

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

### Elimination

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

### Pharmacokinetics in special patient groups

### *Gender*

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

### *Renal impairment*

The AUC of lacosamide was increased by approximately 30 % in mildly and moderately and 60 % in severely renal impaired patients and patients with end-stage renal disease requiring haemodialysis compared to healthy subjects, whereas  $C_{max}$  was unaffected.

Lacosamide is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of lacosamide is reduced by approximately 50 %. Therefore dosage supplementation following haemodialysis is recommended (see section 4.2). The exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

### *Hepatic impairment*

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

### *Elderly (over 65 years of age)*

In a study in elderly men and women including 4 patients > 75 years of age, AUC was about 30 and 50 % increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23 %, respectively. An increased variability in exposure was also observed. The renal clearance of lacosamide was only slightly reduced in elderly subjects in this study.

A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

### *Paediatric population*

The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in two open-label studies in 79 children with epilepsy aged 6 months to 17 years. The administered lacosamide doses ranged from 2 to 12 mg/kg/day (irrespective of the weight band of the child) in twice daily intake, with a maximum of 400 mg/day for children weighing 50 kg or more.

The typical plasma clearance was 1.08 L/h, 1.40 L/h and 1.92 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 adult patients (70 kg body weight).

## **5.3 Preclinical safety data**

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

A safety pharmacology study with intravenous administration of lacosamide in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In anesthetized dogs and Cynomolgus monkeys, at intravenous doses of 15-60 mg/kg, slowing of atrial and ventricular conductivity, atrioventricular block and atrioventricular dissociation were seen.

In the repeated dose toxicity studies, mild reversible liver changes were observed in rats starting at about 3 times the clinical exposure. These changes included an increased organ weight, hypertrophy of

hepatocytes, increases in serum concentrations of liver enzymes and increases in total cholesterol and triglycerides. Apart from the hypertrophy of hepatocytes, no other histopathologic changes were observed.

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

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

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Lacosamide Accord 50 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

##### Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Iron oxide red (E172)  
Iron oxide black (E172)  
Indigo carmine aluminum lake (E132)  
Lecithin (soya)

#### Lacosamide Accord 100 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

##### Tablet coat

Polyvinyl alcohol  
Polyethylene glycol

Talc  
Titanium dioxide (E171)  
Lecithin (soya)  
Iron oxide yellow (E172)

#### Lacosamide Accord 150 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

##### Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Lecithin (soya)  
Iron oxide red (E172)  
Iron oxide black (E172)  
Iron oxide yellow (E172)

#### Lacosamide Accord 200 mg film-coated tablets

##### Tablet core

Microcrystalline cellulose  
Hydroxy propyl cellulose-L  
Hydroxy propyl cellulose (low substituted)  
Silica, colloidal, anhydrous  
Crospovidone  
Magnesium stearate

##### Tablet coat

Polyvinyl alcohol  
Polyethylene glycol  
Talc  
Titanium dioxide (E171)  
Lecithin (soya)  
Indigo carmine aluminum lake (E132)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years.

## **6.4 Special precautions for storage**



This medicinal product does not require any special storage conditions.

#### **6.5 Nature and contents of container**

Lacosamide Accord film-coated tablets are packed in PVC-PVDC/Aluminium blisters. The treatment initiation pack contains 4 cartons, each carton with 14 tablets of 50 mg, 100 mg, 150 mg and 200 mg.

#### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

### **7. MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom.

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 18 September 2017

### **10. DATE OF REVISION OF THE TEXT**

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



## **ANNEX II**

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Ltd  
Sage House  
319 Pinner Road  
North Harrow  
Middlesex  
HA1 4HF  
UNITED KINGDOM

Laboratori Fundacio Dau  
C/ C, 12-14 Pol. Ind. Zona Franca  
08040 Barcelona  
SPAIN

Wessling Hungary Kft.  
Foti ut 56  
1047 Budapest  
HUNGARY

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

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

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

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

### **• Risk Management Plan (RMP)**

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

An updated RMP should be submitted

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

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 50 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 50 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/001  
EU/1/17/1230/002  
EU/1/17/1230/003  
EU/1/17/1230/004  
EU/1/17/1230/017  
EU/1/17/1230/018

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 50 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number}  
SN: {number}  
NN: {number}



**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister label**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 50 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 100 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 100 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/005  
EU/1/17/1230/006  
EU/1/17/1230/007  
EU/1/17/1230/008  
EU/1/17/1230/019  
EU/1/17/1230/020

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 100 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number}  
SN: {number}  
NN: {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister label**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 100 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 150 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 150 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/009  
EU/1/17/1230/010  
EU/1/17/1230/011  
EU/1/17/1230/012  
EU/1/17/1230/021  
EU/1/17/1230/022

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 150 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number}  
SN: {number}  
NN: {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister label**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 150 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 200 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 200 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**



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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/013  
EU/1/17/1230/014  
EU/1/17/1230/015  
EU/1/17/1230/016  
EU/1/17/1230/023  
EU/1/17/1230/024

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 200 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number}  
SN: {number}  
NN: {number}

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister label**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 200 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING  
TREATMENT INITIATION PACK ONLY**

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

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 50 mg  
Lacosamide Accord 100 mg  
Lacosamide Accord 150 mg  
Lacosamide Accord 200 mg  
film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 50 mg  
Lacosamide Accord 100 mg  
Lacosamide Accord 150 mg  
Lacosamide Accord 200 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**TREATMENT INITIATION PACK ONLY**

**Intermediate Carton**

**Carton 14 tablets – week 1**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 50 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 film-coated tablet contains 50 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets.  
Week 1

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**

**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 50 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**TREATMENT INITIATION PACK ONLY**

**Blister label – week 1**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 50 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

Week 1

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**TREATMENT INITIATION PACK ONLY**

**Intermediate Carton**

**Carton 14 tablets – week 2**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 100 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 film-coated tablet contains 100 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets.  
Week 2

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**



**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 100 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**TREATMENT INITIATION PACK ONLY**

**Blister label – week 2**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 100 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

Week 2

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**TREATMENT INITIATION PACK ONLY**

**Intermediate Carton**

**Carton 14 tablets – week 3**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 150 mg film-coated tablets  
lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 film-coated tablet contains 150 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).  
See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets.  
Week 3

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**

**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 150 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**TREATMENT INITIATION PACK ONLY**

**Blister label – week 3**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 150 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

Week 3

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**TREATMENT INITIATION PACK ONLY**

**Intermediate Carton**

**Carton 14 tablets – week 4**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 200 mg film-coated tablets

lacosamide

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 film-coated tablet contains 200 mg lacosamide.

**3. LIST OF EXCIPIENTS**

This medicinal product contains lecithin (soya).

See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets.

Week 4

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP:

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**

**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1230/025

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Lacosamide Accord 200 mg

**17. UNIQUE IDENTIFIER - 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

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

**Blister label – week 4**

**1. NAME OF THE MEDICINAL PRODUCT**

Lacosamide Accord 200 mg film-coated tablets  
lacosamide

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Accord

**3. EXPIRY DATE**

EXP:

**4. BATCH NUMBER**

Lot:

**5. OTHER**

Week 4



**B. PACKAGE LEAFLET**

## **Package leaflet: Information for the patient**

**Lacosamide Accord 50 mg film-coated tablets**  
**Lacosamide Accord 100 mg film-coated tablets**  
**Lacosamide Accord 150 mg film-coated tablets**  
**Lacosamide Accord 200 mg film-coated tablets**  
lacosamide

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

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

### **What is in this leaflet**

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

### **1. What Lacosamide Accord is and what it is used for**

#### **What Lacosamide Accord is**

Lacosamide Accord 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 Lacosamide Accord is used for**

- Lacosamide Accord is used in adults, adolescents and children aged 4 years and older.
- It is used to treat a certain type of epilepsy called “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.
- Lacosamide Accord may be used on its own or with other antiepileptic medicines.

### **2. What you need to know before you take Lacosamide Accord**

#### **Do not take Lacosamide Accord**

- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in section 6). If you are not sure whether you are allergic, please discuss with your doctor
- if you are allergic to peanut or soya.
- if you have a certain type of heart beat problem called second- or third-degree AV block.

Do not take Lacosamide Accord 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 Lacosamide Accord 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. Lacosamide Accord 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 Lacosamide Accord.

### **Children under 4 years**

Lacosamide Accord 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 Lacosamide Accord**

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 Lacosamide Accord 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 Lacosamide Accord.

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 Lacosamide Accord 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;
- a herbal medicine used to treat mild anxiety and depression called St.John’s wort.

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

### **Lacosamide Accord with alcohol**

As a safety precaution do not take Lacosamide Accord 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 Lacosamide Accord if you are pregnant or breast-feeding, as the effects of lacosamide on pregnancy and the unborn baby or the new-born child are not known. Also, it is not known whether Lacosamide Accord 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 Lacosamide Accord 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 Lacosamide Accord may make you feel dizzy or cause blurred vision.

### **Lacosamide Accord contains soya lecithin.**

If you are allergic to peanut or soya, do not use this medicinal product.

## **3. How to take Lacosamide Accord**

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 Lacosamide Accord

- Take Lacosamide Accord 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 Lacosamide Accord tablet with a glass of water.
- You may take Lacosamide Accord 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. Lacosamide Accord is used as a long term treatment. You should continue to take Lacosamide Accord until your doctor tells you to stop.

### **How much to take**

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

#### **Adults, adolescents and children weighing 50 kg or more**

##### When you take Lacosamide Accord on its own

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

Your doctor may also prescribe a starting dose of 100 mg of Lacosamide Accord 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 Lacosamide Accord with other antiepileptic medicines

The usual starting dose of Lacosamide Accord 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 Lacosamide Accord 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 Lacosamide Accord than you should**

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

You may experience:

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

### **If you forget to take Lacosamide Accord**

- 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 Lacosamide Accord 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 Lacosamide Accord**

- Do not stop taking Lacosamide Accord without talking to your doctor, as your epilepsy may come back again or become worse.
- If your doctor decides to stop your treatment with Lacosamide Accord, 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, hand, 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

- Eating less than usual;
- Feeling sleepy or lacking in energy;
- Changes in behaviour, not acting like themselves.

#### **Reporting of side effects**

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

### **5. How to store Lacosamide Accord**

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

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

This medicine does not require any special storage conditions.

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

### **6. Contents of the pack and other information**

#### **What Lacosamide Accord contains**

The active substance is lacosamide.

One tablet of Lacosamide Accord 50 mg contains 50 mg lacosamide.

One tablet of Lacosamide Accord 100 mg contains 100 mg lacosamide.

One tablet of Lacosamide Accord 150 mg contains 150 mg lacosamide.  
One tablet of Lacosamide Accord 200 mg contains 200 mg lacosamide.

The other ingredients are:

*Tablet core:* Microcrystalline cellulose, hydroxy propyl cellulose-L, hydroxy propyl cellulose (low substituted), silica colloidal anhydrous, crospovidone and magnesium stearate.

*Film-coat:* Polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), lecithin (soya) and colorants\*

\* The colorants are

50 mg tablet: Iron oxide red (E172), iron oxide black (E172), indigo carmine aluminum lake (E132)

100 mg tablet: Iron oxide yellow (E172)

150 mg tablet: Iron oxide red (E172), iron oxide black (E172), iron oxide yellow (E172)

200 mg tablet: Indigo carmine aluminum lake (E132)

### **What Lacosamide Accord looks like and contents of the pack**

Lacosamide Accord 50 mg are pink, oval, approximately 10.3 x 4.8 mm, coated tablets, debossed “L” on one side and “50” on other side.

Lacosamide Accord 100 mg are dark yellow, oval, approximately 13.0 x 6.0 mm, coated tablets, debossed “L” on one side and “100” on other side.

Lacosamide Accord 150 mg are salmon, oval, approximately 15.0 x 6.9 mm, coated tablets, debossed “L” on one side and “150” on other side.

Lacosamide Accord 200 mg are blue, oval, approximately 16.4 x 7.6 mm, coated tablets, debossed “L” on one side and “200” on other side.

Lacosamide Accord is available in packs of 14, 56, 60 or 168 film-coated tablets.

The 14 x 1 or 56 x 1 tablet pack is available as perforated unit dose PVC-PVDC/Aluminium blisters sealed with an aluminium foil, all other packs are available with standard PVC-PVDC/Aluminium blisters sealed with an aluminium foil.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

### **Manufacturer**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

or

Wessling Hungary Kft.  
Fóti út 56., Budapest,  
1047, Hungary

or

LABORATORI FUNDACIÓ DAU  
C/ C, 12-14 Pol. Ind. Zona Franca, Barcelona,  
08040 Barcelona, Spain

**This leaflet was last revised in.**

**Other sources of information**

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



## **Package leaflet: Information for the patient**

**Lacosamide Accord 50 mg film-coated tablets**  
**Lacosamide Accord 100 mg film-coated tablets**  
**Lacosamide Accord 150 mg film-coated tablets**  
**Lacosamide Accord 200 mg film-coated tablets**  
lacosamide

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

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

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

### **What is in this leaflet**

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

## **1. What Lacosamide Accord is and what it is used for**

### **What Lacosamide Accord is**

Lacosamide Accord 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 Lacosamide Accord is used for**

- Lacosamide Accord is used in adolescents and children aged 4 years and older weighing 50 kg or more and in adults.
- It is used to treat a certain type of epilepsy called “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.
- Lacosamide Accord may be used on its own or with other antiepileptic medicines.

## **2. What you need to know before you take Lacosamide Accord**

### **Do not take Lacosamide Accord**

- if you are allergic to lacosamide, or any of the other ingredients of this medicine (listed in section 6). If you are not sure whether you are allergic, please discuss with your doctor.
- if you are allergic to peanut or soya.
- if you have a certain type of heart beat problem called second- or third-degree AV block.

Do not take Lacosamide Accord 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 Lacosamide Accord 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. Lacosamide Accord 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 Lacosamide Accord.

### **Children under 4 years**

Lacosamide Accord 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 Lacosamide Accord**

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 Lacosamide Accord 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 Lacosamide Accord.

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 Lacosamide Accord 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 taking Lacosamide Accord.

### **Lacosamide Accord with alcohol**

As a safety precaution do not take Lacosamide Accord with alcohol.

### **Pregnancy and breast-feeding**

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

It is not recommended to take Lacosamide Accord if you are pregnant or breast-feeding, as the effects of lacosamide on pregnancy and the unborn baby or the new-born child are not known.

Also, it is not known whether Lacosamide Accord passes into the 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 Lacosamide Accord 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 Lacosamide Accord may make you feel dizzy or cause blurred vision

### **Lacosamide Accord contains soya lecithin.**

If you are allergic to peanut or soya, do not use this medicinal product.

## **3. How to take Lacosamide Accord**

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 Lacosamide Accord

- Take Lacosamide Accord 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 Lacosamide Accord tablet with a glass of water.
- You may take Lacosamide Accord 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. Lacosamide Accord is used as a long term treatment.

You should continue to take Lacosamide Accord until your doctor tells you to stop.

### **How much to take**

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

### **Adolescents and children weighing 50 kg or more and adults only**

When you take Lacosamide Accord on its own

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

Your doctor may also prescribe a starting dose of 100 mg of Lacosamide Accord 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 Lacosamide Accord with other antiepileptic medicines

Start of the treatment (the first 4 weeks)

This pack (treatment initiation pack) is used when you start your treatment with Lacosamide Accord.

The pack contains 4 different packages for the first 4 weeks of treatment, one package for each week.

Each package has 14 tablets, corresponding to 2 tablets per day for 7 days.

Each package contains a different dosage strength of Lacosamide Accord, so you will increase your dose gradually.

You will start your treatment with a low dose of Lacosamide Accord, usually 50 mg twice a day, and increase it week by week. The usual dose that may be taken per day for each of the first 4 weeks of treatment is shown in the following table. Your doctor will tell you whether you need all 4 packages.

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

<b>Week</b>	<b>Package to be used</b>	<b>First dose (in the morning)</b>	<b>Second dose (in the evening)</b>	<b>TOTAL daily dose</b>
<b>Week 1</b>	Package marked "Week 1"	50 mg (1 tablet Lacosamide Accord 50 mg)	50 mg (1 tablet Lacosamide Accord 50 mg)	100 mg
<b>Week 2</b>	Package marked "Week 2"	100 mg (1 tablet Lacosamide Accord 100 mg)	100 mg (1 tablet Lacosamide Accord 100 mg)	200 mg
<b>Week 3</b>	Package marked "Week 3"	150 mg (1 tablet Lacosamide Accord 150 mg)	150 mg (1 tablet Lacosamide Accord 150 mg)	300 mg
<b>Week 4</b>	Package marked "Week 4"	200 mg (1 tablet Lacosamide Accord 200 mg)	200 mg (1 tablet Lacosamide Accord 200 mg)	400 mg

Maintenance treatment (after the first 4 weeks)

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

#### **Children and adolescents below 50 kg**

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

#### **If you take more Lacosamide Accord than you should**

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

You may experience:

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

#### **If you forget to take Lacosamide Accord**

- 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 Lacosamide Accord 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 Lacosamide Accord**

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

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

#### **4. Possible side effects**

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

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

**Very common:** may affect more than 1 in 10 people

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

**Common:** may affect up to 1 in 10 people

- 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, hand, 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

- Eating less than usual;
- Feeling sleepy or lacking in energy;
- Changes in behaviour, not acting like themselves.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects

not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lacosamide Accord

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

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

This medicine does not require any special storage conditions.

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

## 6. Contents of the pack and other information

### What Lacosamide Accord contains

The active substance is lacosamide.

One tablet of Lacosamide Accord 50 mg contains 50 mg lacosamide.

One tablet of Lacosamide Accord 100 mg contains 100 mg lacosamide.

One tablet of Lacosamide Accord 150 mg contains 150 mg lacosamide.

One tablet of Lacosamide Accord 200 mg contains 200 mg lacosamide.

The other ingredients are:

*Tablet core:* Microcrystalline cellulose, hydroxy propyl cellulose-L, hydroxy propyl cellulose (low substituted), silica colloidal anhydrous, crospovidone and magnesium stearate.

*Film-coat:* Polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171), lecithin (soya) and colorants\*

\* The colorants are

50 mg tablet: Iron oxide red (E172), iron oxide black (E172), indigo carmine aluminum lake (E132)

100 mg tablet: Iron oxide yellow (E172)

150 mg tablet: Iron oxide red (E172), iron oxide black (E172), iron oxide yellow (E172)

200 mg tablet: Indigo carmine aluminum lake (E132)

### What Lacosamide Accord looks like and contents of the pack

Lacosamide Accord 50 mg are pink, oval, approximately 10.3 x 4.8 mm, coated tablets, debossed “L” on one side and “50” on other side.

Lacosamide Accord 100 mg are dark yellow, oval, approximately 13.0 x 6.0 mm, coated tablets, debossed “L” on one side and “100” on other side.

Lacosamide Accord 150 mg are salmon, oval, approximately 15.0 x 6.9 mm, coated tablets, debossed “L” on one side and “150” on other side.

Lacosamide Accord 200 mg are blue, oval, approximately 16.4 x 7.6 mm, coated tablets, debossed “L” on one side and “200” on other side.

The treatment initiation pack contains 56 film-coated tablets in 4 packages:

- the package marked ‘Week 1’ contains 14 tablets of 50 mg,
- the package marked ‘Week 2’ contains 14 tablets of 100 mg,
- the package marked ‘Week 3’ contains 14 tablets of 150 mg,
- the package marked ‘Week 4’ contains 14 tablets of 200 mg .

### Marketing Authorisation Holder

Accord Healthcare Limited

Sage House, 319 Pinner Road,

North Harrow, Middlesex, HA1 4HF  
United Kingdom

**Manufacturer**

Accord Healthcare Limited  
Sage House, 319 Pinner Road,  
North Harrow, Middlesex, HA1 4HF  
United Kingdom

or

Wessling Hungary Kft.  
Fóti út 56., Budapest,  
1047, Hungary

or

LABORATORI FUNDACIÓ DAU  
C/ C, 12-14 Pol. Ind. Zona Franca, Barcelona,  
08040 Barcelona, Spain

**This leaflet was last revised in.**

**Other sources of information**

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