

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

ELEPSI® 200 mg film tablet

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Active ingredient:

Each film tablet contains 200 mg lacosamide.

#### Excipients

Lechitine (soya) 0.350 mg

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film tablet

A blue, biconvex, oval, film tablet

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

ELEPSI® is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in epileptic patients over 16 years of age.

#### 4.2 Posology and method of administration

##### Posology:

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

Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. 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.

Depending on response and tolerability, the maintenance dose can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 400 mg (200 mg twice a day).

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

**The frequency and durations of administration:**

It should be given in two equally divided doses.

**Method of administration:**

ELEPSI<sup>®</sup> is taken orally with or without food.

**Additional Information on Special Populations****Renal impairment**

No dose adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance >30 ml/min). In patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) and in patients with end-stage renal disease, a maximum maintenance dose of 250 mg/day is recommended. In these patients, the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used.

For patients requiring hemodialysis an additional dose up to 50% of the divided daily dose directly after the end of hemodialysis is recommended.

Treatment of patients with end-stage renal disease should be made with caution, since there is limited clinical experience and accumulation of a metabolite (with no known pharmacological activity).

**Hepatic impairment:**

No dose adjustment is needed for patients with mild to moderate hepatic impairment. The dose titration in these patients should be performed with caution considering co-existing renal impairment. A loading dose of 200 mg may be considered, but further dose titration (>200 mg daily) should be performed with caution. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients (see section 5.2).

**Paediatric population:**

Due to the absence of data on the safety and efficacy in patients under 16 years of age, treatment with ELEPSI<sup>®</sup> is not recommended in children and adolescents.

**Geriatric population:**

No dose reduction is necessary in elderly patients.

The experience with lacosamide in elderly patients with epilepsy is limited. Age associated decreased renal clearance with an increase in Area Under Curve (AUC) levels should be considered in elderly patients (see section on “Renal Impairment” and section 5.2).

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients.
- Known second- or third-degree atrioventricular (AV) block.

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

##### **Dizziness**

Treatment with ELEPSI® may be 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).

##### **Cardiac rhythm and conduction**

Prolongations in PR interval with lacosamide have been observed in clinical studies.

ELEPSI® should be used with caution in patients with known conduction problems or severe cardiac disease such as a history of myocardial infarction or heart failure. Caution should especially be exerted when treating elderly patients as they may be at an increased risk of cardiac disorders or when ELEPSI® is used in combination with products known to be associated with PR prolongation.

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.

##### **Suicidal ideation and behaviour**

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptics has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lacosamide. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

ELEPSI® contains lechitine (soy). Patients with peanut or soy allergy should not use this medicinal product.

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

ELEPSI® should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, 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 3A4 to a clinically relevant extent.

Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice daily), but C<sub>max</sub> of midazolam was slightly increased (30%). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, lacosamide given 300 mg twice daily).

The CYP2C19 inhibitor omeprazole (40 mg q.d.) 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.

*Antiepileptics:*

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. A population PK analysis estimated that concomitant treatment with other anti- epileptics 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 ELEPSI<sup>®</sup> 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 drugs through competition for protein binding sites are considered unlikely.

#### **Additional information on special populations**

None.

### **4.6 Pregnancy and lactation**

#### **General recommendation**

Pregnancy category C:

#### **Women of childbearing potential/Birth control (Contraception)**

Women of childbearing potential should be assessed in detail by a physician in terms of the use of an effective contraception method prior to initiation with ELEPSI<sup>®</sup>.

Clinical studies showed no clinically significant interactions between lacosamide and ethinylestradiol or levonorgestrel in oral contraceptives (see Section 4.5).

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

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

#### **Pregnancy**

Data on the use of ELEPSI<sup>®</sup> in pregnant women is inadequate. 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. ELEPSI<sup>®</sup> 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.

#### **Lactation**

It is unknown whether ELEPSI<sup>®</sup> is excreted in human breast milk. Animal studies have shown excretion of lacosamide in breast milk.

For precautionary measures, breast-feeding should be discontinued during treatment with ELEPSI<sup>®</sup>.

### **Ability to reproduce/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.

### **4.7 Effects on ability to drive and use machines**

ELEPSI<sup>®</sup> has minor to moderate influence on the ability to drive and use machines. ELEPSI<sup>®</sup> 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**

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 with ELEPSI<sup>®</sup> 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.

Over all 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.

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.

### **Blood and lymphatic disorders**

Unknown:

- Agranulocytosis<sup>1</sup>

### **Immune system disorders**

Uncommon:

- Drug hypersensitivity<sup>1</sup>

Unknown:

- Drug reaction with eosinophilia and systemic symptoms (DRESS) (1)

### **Psychiatric disorders**

Common:

- Depression
- Confusional state
- Insomnia<sup>1</sup>

Uncommon:

- Aggression<sup>1</sup>
- Agitation<sup>1</sup>
- Euphoric mood<sup>1</sup>
- Psychotic disorder<sup>1</sup>
- Suicide attempt<sup>1</sup>
- Suicidal ideation<sup>1</sup>
- Hallucination<sup>1</sup>

### **Nervous system disorders**

Very common:

- Dizziness
- Headache

Common:

- Balance disorder
- Coordination abnormal
- Memory impairment
- Cognitive disorder
- Somnolence
- Tremor
- Nystagmus
- Hypoesthesia
- Dysarthria
- Disturbance in attention
- Paraesthesia

### **Eye disorders**

Very common:

- Diplopia

Common:

- Vision blurred

### **Ear and labyrinth disorders**

Common:

- Vertigo
- Tinnitus

### **Cardiac disorders**

Uncommon:

- Atrioventricular block<sup>1</sup>
- Bradycardia<sup>1</sup>
- Atrial Fibrillation<sup>1</sup>
- Atrial Flutter<sup>1</sup>

**Gastrointestinal disorders**

Very common:

- Nausea

Uncommon:

- Vomiting
- Constipation
- Flatulence
- Dyspepsia
- Dry mouth
- Diarrhoea

**Hepato-biliary disorders**

Uncommon:

- Liver function test abnormality<sup>1</sup>

**Skin and subcutaneous tissue disorders**

Common

- Pruritus
- Rash<sup>1</sup>

Uncommon

- Angioedema<sup>1</sup>
- Urticaria

Unknown:

- Stevens-Johnson syndrome<sup>1</sup>
- Toxic epidermal necrolysis

**Musculo-skeletal tissue, connective tissue, and bone disorders**

Common

- Muscle spasm

**General disorders and disorders of the site of administration**

Common

- Gait disorder
- Asthenia
- Fatigue
- Irritability
- Dizziness

**Injuries, toxicity and procedures-related complications**

Common:

- Falls
- Skin wounds
- Contusion

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

### Description of selected adverse reactions

The use of ELEPSI<sup>®</sup> 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 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 clinical trials, the incidence rate for syncope is uncommon and did not differ between lacosamide treated epilepsy patients (0.1%) and placebo treated epilepsy patients (0.3%).

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 anti-epileptic drugs. Elevations of ALT to  $\geq 3 \times \text{ULN}$  occurred in 0.7% (7/935) of ELEPSI<sup>®</sup> 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 agents. 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.

### Pediatric Population:

Frequency, type and severity of adverse reactions in adolescents aged 16-18 years are expected to be the same as in adults. The safety of lacosamide in children aged below 16 years has not yet been established. No data are available.

### **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 to Turkish Center of Pharmacovigilance (TUFAM) ([www.titck.gov.tr](http://www.titck.gov.tr); e-mail: [tufam@titck.gov.tr](mailto:tufam@titck.gov.tr); tel: 0 800 314 00 08; faks: 0 312 218 35 99).

## **4.9 Overdose and its treatment**

### Symptoms

#### In clinical trials

The types of adverse events experienced by patients exposed to supratherapeutic doses were not clinically different from those of patients administered recommended doses of lacosamide.

Following doses of 1,200 mg/day, symptoms related to the central nervous system (e.g. dizziness) and the gastrointestinal system (e.g. nausea, vomiting) were observed and resolved with dose adjustments.

The highest reported overdose for lacosamide was 12,000 mg taken in conjunction with toxic doses of multiple other antiepileptics drugs. The subject was initially comatose with AV block and then fully recovered without permanent sequelae.

In post-marketing experience

Following acute single overdoses ranging between 1,000 mg and 12,000 mg, seizures (generalized tonic-clonic seizures, status epilepticus) and cardiac conduction disorders were observed. Fatal cardiac arrest was reported after an acute overdose of 7,000 mg of lacosamide in a patient with cardiovascular risk factors.

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

The active substance, lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide), functional amino aside.

#### Mechanism of action:

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 generalized 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:

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 1308 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 antiepileptics 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.

There are insufficient data regarding the withdrawal of concomitant antiepileptic medicinal products to achieve monotherapy with lacosamide.

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

## **5.2 Pharmacokinetic properties**

### **General Properties**

#### Absorption

Lacosamide is rapidly and completely absorbed after oral administration. The oral bioavailability of ELEPSI<sup>®</sup> tablets is approximately 100%. Following oral administration, the plasma concentration of unchanged lacosamide increases rapidly and reaches C<sub>max</sub> about 0.5 to 4 hours post-dose. ELEPSI<sup>®</sup> tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

#### Distribution

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

#### Biotransformation

95% of the dose is excreted in the urine as drug 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 known 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 feces. The elimination half-life of the unchanged drug 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.

### Linearity/Non-linearity:

Lacosamide pharmacokinetics is dose-proportional and consistent over time with low intra- and inter-individual variability.

### **Special populations**

#### Age:

Geriatric population: 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).

#### 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 endstage renal disease requiring hemodialysis 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 endstage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in endstage 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<sub>norm</sub>). 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).

### **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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Microcrystalline cellulose

Hydroxypropyl cellulose

Hydroxypropyl cellulose (low substituted)

Prosolv HD90

Crospovidone

Colloidal silicon dioxide

Magnesium stearate

Polyvinyl alcohol-part. Hydrolyzed

Talc

Titanium dioxide

Macragol  
Indigo carmine aluminum salt  
Lechitin (soya)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

24 months.

## **6.4 Special precautions for storage**

Keep in room temperature below 25°C

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

Packs of 56 film tablets in PVC/PE/PVDC folio blister together with prescription information.

## **6.6 Disposal of unused medications and other special precautions**

Unused medications should be disposed of in accordance with the “Regulations for the Control of Medical Waste” and “Regulations for the Control of Packs and Pack Waste”

## **7. MARKETING AUTHORISATION HOLDER**

Santa Farma İlaç San. A.Ş.  
Okmeydanı, Boruçiçeği Sok. No: 16  
34382 Şişli- İSTANBUL  
0212 220 64 00  
0212 222 57 59

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

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

Date of first authorization:--

Date of latest renewal:---

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

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