SEIZGARD™ Film Coated Tablets
(Lacosamide Tablets Ph. Eur.)
Prescribing Information

NAME OF THE MEDICINAL PRODUCT

Seizgard (Lacosamide Tablets Ph. Eur.) 50 mg film-coated tablets
Seizgard (Lacosamide Tablets Ph. Eur.) 100 mg film-coated tablets
Seizgard (Lacosamide Tablets Ph. Eur.) 150 mg film-coated tablets
Seizgard (Lacosamide Tablets Ph. Eur.) 200 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Lacosamide Ph. Eur.....50 mg
Colours: Iron oxide Red & Titanium dioxide IP

Each film coated tablet contains
Lacosamide Ph. Eur .....100 mg
Colours: Iron oxide Yellow & Titanium dioxide IP

Each film coated tablet contains
Lacosamide Ph. Eur.....150 mg
Colours:
Iron oxide Yellow, Iron oxide Red, Iron oxide Black & Titanium Dioxide IP

Each film coated tablet contains
Lacosamide Ph. Eur.....200 mg
Colours: Indigo carmine aluminum lake & Titanium dioxide IP

PHARMACEUTICAL FORM

Seizgard 50 mg film-coated tablet: pink, round, film-coated tablet.
Seizgard 100 mg film-coated tablet: yellow, round, film-coated tablet.
Seizgard 150 mg film-coated tablet: tan, caplet film-coated tablet.
Seizgard 200 mg film-coated tablet: blue, caplet film-coated tablet.

CLINICAL PARTICULARS

Therapeutic Indications

Seizgard (lacosamide) tablets are indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy >17 years of age.

Posology and method of administration

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

Dose Adjustment
Partial-Onset Seizures
The initial dose should be 50 mg twice daily (100 mg per day) which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. Based on individual patient response and tolerability, the maintenance dose can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day,

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).

CONTRA-INDICATIONS

In patients with known or suspected hypersensitivity to any of the ingredients of this product.
Known second- or third-degree atrioventricular (AV) block.

Special Populations

Pregnancy
Risk related to epilepsy and antiepileptic medicinal products in general
For all antiepileptic medicinal products, it has been shown that in the offspring of 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. 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).

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.

Renal Impairment
No dose adjustment is necessary in mildly and moderately renally impaired patients (CL_{CR} > 30 ml/min). 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 patients with mild to moderate hepatic impairment.
The dose titration in these patients should be performed with caution considering co-existing renal impairment. The pharmacokinetics of lacosamide has not been evaluated in severely hepatic impaired patients. Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.
Gender
Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of lacosamide.

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.

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

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.

Second-degree or higher AV block has been reported in post-marketing experience. In the placebo-controlled trials of lacosamide in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy trials and in post-marketing experience.
Patients should be made aware of the symptoms of second-degree or higher AV block (e.g. slow or irregular pulse, feeling of lightheaded and fainting) and of the symptoms of atrial fibrillation and flutter (e.g. palpitations, rapid or irregular pulse, shortness of breath). Patients should be counselled to seek medical advice should any of these symptoms occur.

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 3A4 to a clinically relevant extent. Lacosamide did not affect the AUC of midazolam (metabolised by CYP3A4, lacosamide given 200 mg twice a day), but Cmax of midazolam was slightly increased (30 %). Lacosamide did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and 3A4, 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.

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 (≥ 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.

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

System organ class	Very common	Common	Uncommon	Not known
Blood and lymphatic disorders				Agranulocytosis[1]
Immune system disorders			Drug hypersensitivity[1]	Drug reaction with eosinophilia and systemic symptoms (DRESS)[1,2]
Psychiatric disorders		Depression Confusional state Insomnia[1]	Aggression Agitation[1] Euphoric mood[1] Psychotic disorder[1] Suicide attempt[1] Suicidal ideation Hallucination[1]	
Nervous system disorders	Dizziness Headache	Balance disorder Coordination abnormal Memory impairment Cognitive disorder Somnolence Tremor Nystagmus Hypoesthesia Dysarthria Disturbance in attention Paraesthesia	Syncope[2]	Convulsion
Eye disorders	Diplopia	Vision blurred		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders			Atrioventricular block[1,2] Bradycardia[1,2] Atrial Fibrillation[1,2] Atrial Flutter[1,2]	
Gastrointestinal disorders	Nausea	Vomiting Constipation Flatulence Dyspepsia Dry mouth Diarrhoea		
Hepatobiliary disorders			Liver function test abnormal[2] Hepatic enzyme increased (> 2x ULN)[1]	
Skin and subcutaneous tissue disorders		Pruritus Rash[1]	Angioedema[1] Urticaria[1]	Stevens-Johnson syndrome[1] Toxic epidermal necrolysis[1]
Musculoskeletal and connective tissue disorders		Muscle spasms		
General disorders and administration site conditions		Gait disturbance Asthenia Fatigue Irritability Feeling drunk		
Injury, poisoning and procedural complications		Fall Skin laceration Contusion		

[1] Adverse reactions reported in post marketing experience.
[2] See Description of selected adverse reactions.

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 postmarketing experience.

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

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

Effects on ability to drive and use machines
- Lacosamide has minor to moderate influence on the ability to drive and use ma chines. 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 laco amide on their ability to perform such activities.

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.

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

PHARMACEUTICAL PARTICULARS
List of excipients
Tablet core
microcrystalline cellulose
hydroxypropylcellulose
hydroxypropylcellulose (low substituted)
silica, colloidal, anhydrous
crospovidone (polyplasdone XL-10 Pharmaceutical Grade)
magnesium stearate

Tablet coat

Seizgard 50 mg film-coated tablets Opadry II Pink 85F34324*	Seizgard 100 mg film-coated tablets Opadry II Yellow 85G52072*
Seizgard 150 mg film-coated tablets Opadry II Tan 85G27190*	Seizgard 200 mg film-coated tablets Opadry II Blue 85G20458*

Incompatibilities
Not applicable.

Storage
This medicinal product does not require any special storage conditions.
Keep out of reach of children.

Nature and contents of container
Seizgard 50 mg, 100 mg, 150 mg and 200 mg film-coated tablet - available in blister pack.

Special precautions for disposal
No special requirements for disposal.

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B31354-01

MARKETED BY:

UCB INDIA PVT. LTD
BLDG. NO. P3, UNIT NO. 103,
FIRST FLOOR, PRITHVI COMPLEX, KALHER PIPELINE,
KALHER, BHIWANDI – 421302.

Version 3.0 dated 4th May 2018

UCB Artwork number : CIA02187/88/89/90/91/92-PI-03