AUSTRALIAN PRODUCT INFORMATION

VIMPAT (LACOSAMIDE) FILM-COATED TABLETS AND ORAL SOLUTION

1 NAME OF THE MEDICINE

Lacosamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vimpat film-coated tablets are available in strengths of 50 mg, 100 mg, 150 mg and 200 mg lacosamide. Vimpat oral solution is available as 10 mg/mL strength.

Vimpat oral solution contains the following excipients: sorbitol and hydroxybenzoates. For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Film-coated tablets

50 mg: Pinkish, oval debossed with ‘SP’ on one side and ‘50’ on the other side.

100 mg: Dark yellow, oval debossed with ‘SP’ on one side and ‘100’ on the other side.

150 mg: Salmon, oval debossed with ‘SP’ on one side and ‘150’ on the other side.

200 mg: Blue, oval debossed with ‘SP’ on one side and ‘200’ on the other side.

Oral Solution

Colourless to yellow or yellow brown liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vimpat (lacosamide) tablets and oral solution are indicated as:

- monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.
- add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 4 years and older.
- add-on therapy in the treatment of primary generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy aged 4 years and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

Vimpat therapy can be initiated with either oral or IV administration. The oral solution may be diluted in a glass of water. Both the film-coated tablets and oral solution may be taken with or without food.

The film-coated tablets must not be divided.

A nasogastric tube or gastrostomy tube may be used when administering the oral solution. The nasogastric tube or gastrostomy tube should be flushed (twice the volume of dead space) after the product delivery to ensure the correct the dose of lacosamide is administered.

Conversion to or from oral and IV administration can be done directly without titration. The total daily dose and twice daily administration should be maintained.

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

The following table summarises the recommended dose for Vimpat tablets and oral solution. More details are provided below.

	Monotherapy (partial-onset seizures)		**Add-on therapy (partial-onset seizures or primary generalised tonic-clonic seizures)**	
	Adults	**Adolescents below 16 years and children**	**Adolescents and children weighing 50 kg or more, and adults**	**children (from 4 years of age or adolescents weighing less than 50kg**
Starting dose	200 mg/day	NOT INDICATED	100 mg/day	2 mg/kg/day
Single loading dose (if applicable)	200 mg		200 mg	NOT RECOMMENDED
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	2 mg/kg/day every week
Maximum recommended dose	up to 600 mg/day		up to 400 mg/day	• up to 12 mg/kg/day (in children weighing < 30 kg) • up to 8 mg/kg/day (in children weighing from 30 to under 50 kg)
Conversion to monotherapy	gradual withdrawal of the concomitant antiepileptic drugs over at least 6 weeks is recommended		NOT INDICATED (except for adults, see first column)	NOT INDICATED

Adults

Monotherapy (partial-onset seizures)

Vimpat must be taken twice a day. The recommended starting dose is 100 mg twice a day.

Depending on response and tolerability, the dose can be further increased by 50 mg twice a day every week, to a maximum recommended daily dose of 600 mg (300 mg twice a day).

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

Add-on Therapy (partial-onset seizures or primary generalised tonic-clonic seizures)
Vimpat must be taken twice a day. The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

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

Add-on Therapy converting to monotherapy (partial-onset seizures)
For patients on add-on therapy who will convert to lacosamide monotherapy, once the maintenance dose has been administered for at least 3 days, a gradual withdrawal of the concomitant antiepileptic drugs over at least 6 weeks is recommended. If the patient is on more than one antiepileptic drug, the antiepileptic drugs should be withdrawn sequentially. Safety and efficacy of lacosamide have not been established for simultaneous conversion to monotherapy from two or more concomitant antiepileptic drugs.

Initiation of lacosamide treatment with a loading dose (partial-onset seizures or primary generalised tonic-clonic seizures)
Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustment should be performed according to individual response and tolerability as described above. A loading dose should be administered under medical supervision with consideration of the lacosamide pharmacokinetics (see Section 5.2 Pharmacokinetic properties) and the potential for increased incidence of CNS adverse reactions (see Section 4.8 Adverse Effects (Undesirable effects)). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.

Use in children
Lacosamide is **not indicated** for monotherapy in children and is **not recommended** for use in children below the age of 4 as there is limited data on safety and efficacy in these age groups. The physician should prescribe the most appropriate formulation and strength according to weight and dose.

The dosage in children and adolescents is based on PK modelling targeting plasma concentrations in the same range as in adults.

Add-on therapy (partial-onset seizures or primary generalised tonic-clonic seizures)
<u>Adolescents and children weighing 50 kg or more</u>
Dosage is the same as in adults (see above).

<u>Children from 4 years of age or adolescents weighing less than 50kg)</u>
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. In children weighing less than 30 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 30 to under 50 kg, a maximum dose of 8 mg/kg/day is recommended, although in open-label studies (see Section 4.8 Adverse effects (Undesirable effects) and Section 5.2 Pharmacokinetic properties) a dose up to 12 mg/kg/day has been used by a small number of these children. The maintenance dose should be gradually adjusted until the optimal response is obtained.

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

Loading dose
Loading dose has not been studied in children.

However, **for add-on therapy** in adolescents or children weighing 50 kg or greater, lacosamide treatment may also be initiated with a single loading dose. Dosage is the same as in adults (see above). A loading dose should be administered under medical supervision with consideration of the lacosamide pharmacokinetics (see Section 5.2 Pharmacokinetic properties) and the potential for increased incidence of CNS adverse reactions (see Section 4.8 Adverse effects (Undesirable effects)). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.

Use in patients with impaired renal function
No dose adjustment is necessary in mild to moderate renally impaired adult patients (Cl_{Cr} > 30 mL/min). Based on data in adults, no dose adjustment is necessary in paediatric patients with mild to moderate renal impairment (CLCR >30 ml/min). A maximum dose of 250 mg/day is recommended for adult patients with severe renal impairment ($Cl_{Cr} \leq 30$ mL/min) and in adult patients with end-stage renal disease. In paediatric patients with severe renal impairment (CLCR ≤30 ml/min) and in those with endstage renal disease, a reduction of 25% of the maximum dose is recommended. For patients requiring haemodialysis a supplement of up to 50% of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity). In all patients with renal impairment, the dose titration should be performed with caution (see Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special patient groups).

Use in patients with impaired hepatic function
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 coexisting renal impairment. Based on data in adults, in paediatric patients 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 Pharmacokinetic Properties, Pharmacokinetics in special patient groups). Lacosamide should be administered to patients with severe hepatic impairment only when the expected therapeutic benefits outweigh the possible risks, and the dosage and administration need to be adjusted while carefully observing the symptoms of patient.

Use in elderly (65 years and older)
No dose reduction is necessary in elderly patients. Age associated decreased renal clearance should be considered in elderly patients (see 'Use in patients with impaired renal function' above and Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special patient groups).

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

Vimpat (lacosamide) oral solution contains aspartame, a source of phenylalanine, which may be harmful for people with phenylketonuria.

Suicidal behaviour and ideation
Antiepileptic drugs, including lacosamide, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 - Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo patients with events/1000 patients	Drug patients with events/1000 patients	Relative Risk: Incidence of events in Drug patients/incidence in Placebo patients	Risk Difference: Additional Drug patients with events per 1000 patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing lacosamide or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence of worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self harm. Behaviours of concern should be reported immediately to the treating doctor.

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 medication (see Section 4.8 Adverse Effects (Undesirable Effects)).

Cardiac rhythm and conduction
Dose dependent prolongations in PR interval with Vimpat were observed in clinical studies. When Vimpat is given with other drugs that prolong the PR interval, further PR prolongation is possible.

Vimpat should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischemia/ infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blockers (see Section 4.5 Interaction with Other Medicines). In such patients, obtaining an ECG before beginning Vimpat, and after Vimpat is titrated to steady-state, is recommended.

Vimpat may predispose patients with diabetic neuropathy and/or cardiovascular disease to atrial arrhythmias (atrial fibrillation or flutter).

In the placebo-controlled trials of Vimpat 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 Adverse Effects (Undesirable Effects), Post-marketing experience). In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been rarely reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular

pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if these symptoms occur.

In patients who develop serious cardiac arrhythmia, lacosamide should be discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

Discontinuation
In accordance with current clinical practice, if Vimpat has to be discontinued in patients with partial-onset seizures, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Use with alcohol
No data on the interaction of lacosamide with alcohol are available.

Non-clinical cardiac safety
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.

Use in hepatic impairment
See Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties.

Use in renal impairment
See Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties.

Use in the elderly
The experience with lacosamide in elderly patients with epilepsy is limited. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see Section 5.2 Pharmacokinetic Properties, Renal impairment).

Paediatric use
Vimpat is not recommended for use in children under 4 years of age.

Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (based on AUC) below that in humans at the maximum recommended dose. In juvenile dogs, transient CNS clinical signs were similar to those observed in adult dogs. Non-adverse microscopic changes (commonly reported in juvenile dogs and of unkown clinical significance) were seen in the periventricular region. Both findings were associated with lacosamide exposures (based on AUC) below those anticipated clinically at the maximum recommended dose. Thus, potential adverse effects on CNS development cannot be ruled out.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lacosamide should be used with caution in patients treated with medicinal products known to be associated with PR prolongation (including sodium channel blocking antiepileptic drugs such as carbamazepine, lamotrigine and pregabalin) and, in patients treated with antiarrhythmic drugs. However, subgroup analysis in clinical trials did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

In vitro data

Data generally suggest that lacosamide has a low interaction potential. *In vitro* metabolism studies indicate that lacosamide does not induce the enzyme activity of drug metabolizing cytochrome P450 isoforms CYP1A2, 2B6, 2C9 and 3A4. Lacosamide did not inhibit CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 and 3A4/5 at plasma concentrations observed in clinical trials. *In vitro* data suggest that lacosamide has the potential to inhibit CYP2C19 at therapeutic concentrations.

Lacosamide was not a substrate or inhibitor for P-glycoprotein.

In vivo data

Clinical data indicate that lacosamide does not inhibit or induce CYP2C19 and 3A4. Furthermore an interaction trial with omeprazole (CYP2C19 inhibitor) demonstrated no clinically relevant changes in lacosamide plasma concentrations and no inhibitory effect on omeprazole pharmacokinetics.

Since < 15% of lacosamide is bound to plasma proteins, a clinically relevant interaction with other drugs through competition for protein binding sites is unlikely.

Antiepileptic drugs

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.

The placebo-controlled clinical studies in patients with partial-onset seizures showed that steady-state plasma concentrations of levetiracetam, carbamazepine, carbamazepine epoxide, lamotrigine, topiramate, oxcarbazepine monohydroxy derivative (MHD), phenytoin, valproic acid, phenobarbital, gabapentin, clonazepam and zonisamide were not affected by concomitant intake of lacosamide at any dose.

Population PK analyses in different age groups estimated that concomitant treatment with other antiepileptic drugs 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 interaction between lacosamide and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were coadministered.

Others

Interaction trials showed that lacosamide had no effect on the pharmacokinetics of digoxin. There was

no clinically relevant interaction between lacosamide and metformin.

Omeprazole 40 mg q.d. increased the AUC of lacosamide by 19%. The effect probably lacks clinical relevance. Lacosamide did not affect the single dose pharmacokinetics of omeprazole.

Coadministration of warfarin with lacosamide does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamic effects of warfarin.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no human data on the effects of lacosamide on male or female fertility. Male or female fertility in rats was unaffected by oral lacosamide doses resulting in an estimated drug exposure (based on plasma $AUC_{0\text{-}24\ h}$) that was one to two times that in humans with the maximum recommended dose. Test doses were limited by CNS adverse effects.

Use in pregnancy
(Category B3)

There are no adequate data from the use of lacosamide in pregnant women. 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 bodyweights were observed at maternal toxic doses in rats corresponding to systemic exposure levels below the expected clinical exposure. Test doses were limited by CNS adverse effects.

Lacosamide and/or its metabolites were shown to cross the placental barrier in rats after treatment of dams, and foetal tissue concentrations were similar to those for maternal tissue.

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. To monitor outcome of pregnancy in women exposed to Vimpat, doctors are encouraged to register pregnant patients taking Vimpat on the Australian Pregnancy Register for Women on Antiepileptic Medication with Epilepsy and Allied Conditions by calling 1800 069 722.

Use in lactation
Lacosamide is excreted in human breast milk. A decision on whether to continue/ discontinue breast-feeding or to continue/ discontinue therapy with Vimpat should be made taking into account the benefit of breast-feeding to the child and the benefit of Vimpat therapy to the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Vimpat may have minor to moderate influence on the ability to drive and use machines. Vimpat treatment has been associated with dizziness or blurred vision. Accordingly, patients should be

advised not to drive a car or to operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical studies

Partial-onset seizures - Add-on therapy

Based on the analysis of pooled placebo-controlled clinical trials 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 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 CNS and gastrointestinal (GI) adverse reactions usually decreased over time. Overall in 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.

The table below shows the incidence of very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions by randomized treatment group which have been reported in pooled placebo-controlled clinical trials.

Table 2 - Incidence of Treatment-Emergent Adverse Events regardless of causality during the Treatment Phase

MedDRA® SOC/ preferred term	Placebo N=364	LCM 200mg/day N=270	LCM 400mg/day N=471	LCM 600mg/day N=203	LCM Total N=944
	n (%)				
Ear and labyrinth disorder					
Vertigo	3 (0.8)	13 (4.8)	14 (3.0)	9 (4.4)	36 (3.8)
Eye disorders					
Diplopia	7 (1.9)	17 (6.3)	49 (10.4)	33 (16.3)	99 (10.5)
Vision blurred	8 (2.2)	6 (2.2)	40 (8.5)	33 (16.3)	79 (8.4)
Gastrointestinal disorders					
Nausea	16 (4.4)	20 (7.4)	53 (11.3)	35 (17.2)	108 (11.4)
Vomiting	9 (2.5)	16 (5.9)	40 (8.5)	32 (15.8)	88 (9.3)
Constipation	3 (0.8)	3 (1.1)	7 (1.5)	8 (3.9)	18 (1.9)
Flatulence	0	7 (2.6)	8 (1.7)	1 (0.5)	16 (1.7)
General disorders and administration site conditions					
Fatigue	20 (5.5)	19 (7.0)	33 (7.0)	30 (14.8)	82 (8.7)
Gait disturbance	1 (0.3)	2 (0.7)	11 (2.3)	9 (4.4)	22 (2.3)
Asthenia	2 (0.5)	4 (1.5)	9 (1.9)	8 (3.9)	21 (2.2)
Injury, poisoning and procedural complications					
Skin laceration	6 (1.6)	6 (2.2)	14 (3.0)	6 (3.0)	26 (2.8)
Fall	1 (0.3)	2 (0.7)	10 (2.1)	2 (1.0)	14 (1.5)
Nervous system disorders					
Dizziness	29 (8.0)	43 (15.9)	139 (29.5)	107 (52.7)	289 (30.6)
Headache	32 (8.8)	30 (11.1)	65 (13.8)	25 (12.3)	120 (12.7)
Coordination abnormal	6 (1.6)	11 (4.1)	34 (7.2)	31 (15.3)	76 (8.1)
Somnolence	17 (4.7)	14 (5.2)	38 (8.1)	16 (7.9)	68 (7.2)
Tremor	15 (4.1)	10 (3.7)	29 (6.2)	24 (11.8)	63 (6.7)
Nystagmus	14 (3.8)	6 (2.2)	21 (4.5)	21 (10.3)	48 (5.1)
Balance disorder	0	3 (1.1)	24 (5.1)	13 (6.4)	40 (4.2)
Memory impairment	6 (1.6)	3 (1.1)	7 (1.5)	12 (5.9)	22 (2.3)
Cognitive disorder	1 (0.3)	1 (0.4)	10 (2.1)	4 (2.0)	15 (1.6)
Psychiatric disorders					
Depression	2 (0.5)	6 (2.2)	11 (2.3)	3 (1.5)	20 (2.1)
Skin and subcutaneous disorders					
Pruritus	2 (0.5)	8 (3.0)	9 (1.9)	5 (2.5)	22 (2.3)

LCM=lacosamide; MedDRA® =Medical Dictionary for Regulatory Activities; SOC=system organ class.
Note: Treatment Phase includes both Titration and Maintenance Phase data.

Effect on liver function tests

Abnormalities in liver function tests have been observed in controlled trials with Vimpat in adult patients with partial-onset seizures who were taking 1 to 3 concomitant antiepileptic drugs. Elevations of ALT to ≥ 3 x ULN occurred in 0.7% (7/935) of Vimpat patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases > 20 x ULN was observed in one healthy subject 10 days after Vimpat treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without

specific treatment. At the time of this event, bilirubin was normal. The hepatitis/ nephritis was interpreted as a delayed hypersensitivity reaction to Vimpat.

Partial-onset seizures - Monotherapy

Based on the analysis of data from a non-inferiority monotherapy clinical trial comparing lacosamide to carbamazepine controlled release (CR), the most common adverse reactions for lacosamide were headache (13.7%), dizziness (11.7%). The discontinuation rate due to adverse reactions was 10.6% for patients randomized to lacosamide and 15.6% for patients randomized to carbamazepine CR.

Table 3 – Incidence of the most commonly reported Treatment-Emergent Adverse Events regardless of causality with onset during the Treatment Period with an incidence of at least 3% in either treatment group

MedDRA® SOC PT	**LCM N=444 n (%) [#]**	**CBZ-CR N=442 n (%) [#]**
Any TEAEs	**328 (73.9) [1212]**	332 (75.1) [1374]
Gastrointestinal disorders		
Nausea	26 (5.9) [32]	22 (5.0) [28]
Diarrhoea	9 (2.0) [11]	17 (3.8) [20]
Constipation	3 (0.7) [3]	19 (4.3) [20]
General disorders and administration site conditions		
Fatigue	32 (7.2) [36]	46 (10.4) [52]
Infections and infestations		
Nasopharyngitis	26 (6.3) [40]	29 (6.6) [36]
Urinary tract infection	13 (2.9) [16]	15 (3.4) [19]
Investigations		
ALT increased	8 (1.8) [9]	15 (3.4) [16]
GGT increased	7 (1.6) [8]	36 (8.1) [37]
Metabolism and nutrition disorders		
Hypercholesterolaemia	11 (2.5) [11]	21 (4.8) [21]
Nervous system disorders		
Headache	61 (13.7) [81]	57 (12.9) [75]
Dizziness	52 (11.7) [60]	38 (8.6) [47]
Somnolence	24 (5.4) [25]	41 (9.30 [46]
Skin and subcutaneous tissue disorders		
Rash	7 (1.6) [11]	14 (3.2) [16]

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 add-on 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 lacosamide treated epilepsy patients. In the monotherapy trial the incidence of prolonged PR intervals was similar across treatment groups: 40 subjects (9.6%) in the lacosamide treatment group and 37 subjects (8.9%) in the carbamazepine CR treatment group experienced a treatment-emergent PR interval of > 200ms and 16 subjects (3.7%) in the lacosamide treatment group and 13 subjects (3.0%) in the carbamazepine CR treatment group experienced a treatment-emergent PR interval of > 220ms. Three subjects in each treatment group (0.7% in each treatment group) experienced a PR interval of > 250ms.

The incidence rate for syncope reported in pooled add-on therapy clinical trials is uncommon and did not differ between lacosamide treated (n=944) epilepsy patients (0.1%) and placebo treated (n=364)

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 1/442 (0.2%) carbamazepine CR patients.

In the short-term investigational trials of lacosamide in epilepsy patients, there were no cases of atrial fibrillation or flutter, however both have been reported in open label epilepsy trials.

In addition, the following potentially important adverse drug reactions have been identified as being reported in clinical trials.

Psychiatric disorders. Common: confusional state, insomnia
Nervous system disorders. Common: myoclonic epilepsy, ataxia, hypoesthesia, dysarthria, disturbance in attention, paraesthesia
Ear and labyrinth disorders. Common: tinnitus
Gastrointestinal disorders. Common: dyspepsia, dry mouth, diarrhoea
General disorders and administration site conditions. Common: irritability, feeling drunk
Musculoskeletal and connective tissue disorders. Common: muscle spasms
Injury, poisoning and procedural complications. Common: contusion

Primary generalised tonic-clonic seizures
The safety profile of lacosamide reported in a study conducted in patients aged 4 years and older with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures (PGTCS) was consistent with the safety profile reported from the pooled placebo-controlled clinical trials in partial-onset seizures. Additional adverse reaction reported in PGTCS patients was myoclonic epilepsy (2.5% in the lacosamide-group and 0% in the placebo-group). The most frequently reported adverse reactions were dizziness and somnolence. The most common adverse reactions resulting in discontinuation of lacosamide therapy were dizziness and suicidal ideation. The discontinuation rate due to adverse reactions was 9.1% of the lacosamide group and 4.1% in the placebo group.

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

Elderly population
In the monotherapy study comparing lacosamide to carbamazepine CR, the safety profile of lacosamide in elderly patients (≥ 65 years of age) appears to be similar to that observed in patients less than 65 years of age. However, a higher incidence (≥5% difference) of fall, diarrhea and tremor has been reported in elderly patients compared to younger adult patients.

Paediatric population
The safety profile of lacosamide in placebo-controlled and in open-label studies in add-on therapy in children from 4 years of age was consistent with the safety profile observed in adults. In a 16 week placebo-controlled study (n=343), the most common adverse reactions were somnolence (14.0%) and, as commonly observed in the paediatric population a high incidence of infections and associated symptoms, such as nasopharyngitis (9.9%), pyrexia (8.2%) and pharyngitis (4.7%). The discontinuation rate during the treatment period due to adverse reactions was 4.1% for patients randomized to lacosamide and 5.8% for patients randomized to placebo. In the placebo-controlled study, the additional adverse reactions reported in children, decreased appetite and lethargy were observed at the rate of 3.5%, 0.6% respectively, and no cases of abnormal behaviour were reported. In

the open-label studies (n=408) with a duration of up to 2 years, these adverse reactions were reported at the rate of 5.9% for decreased appetite, 2.7% for lethargy and 1.7% for abnormal behaviour. In these open-label studies, the most frequently reported adverse reactions were nasopharyngitis (15.7%), vomiting (14.7%), dizziness (13.5), and pyrexia (13.0%). The table below shows the incidence of treatment-emergent adverse event occurred in ≥3% of all children aged from 4 years in the placebo-controlled trial.

Table 4 - Incidence of Treatment-Emergent Adverse Events regardless of causality during the treatment phase in children aged from 4 years of age

MedDRA® SOC/ preferred term	Placebo n=172 n (%)	LCM n=171 n (%)
Any TEAEs	100 (58.1)	116 (67.8)
Eye disorders		
Diplopia	1 (0.6)	8 (4.7)
Gastrointestinal disorders		
Vomiting	7 (4.1)	15 (8.8)
Diarrhoea	7 (4.1)	7 (4.1)
Nausea	5 (2.9)	6 (3.5)
General disorders and administration site conditions		
Pyrexia	7 (4.1)	14 (8.2)
Fatigue	3 (1.7)	7 (4.1)
Infections and infestations		
Nasopharyngitis	7 (4.1)	17 (9.9)
Upper respiratory tract infection	10 (5.8)	8 (4.7)
Pharyngitis	4 (2.3)	8 (4.7)
Metabolism and nutrition disorders		
Decreased appetite	1 (0.6)	6 (3.5)
Nervous system disorders		
Somnolence	9 (5.2)	24 (14.0)
Dizziness	6 (3.5)	18 (10.5)
Headache	11 (6.4)	11 (6.4)
Convulsion	7 (4.1)	4 (2.3)
Tremor	0 (0)	6 (3.5)

LCM=lacosamide; MedDRA® =Medical Dictionary for Regulatory Activities; SOC=system organ class.
Note: n is the number of subjects reporting at least 1 TEAE within system organ class/preferred term.

In addition, the following adverse drug reactions have been identified as being reported in clinical trials.

Psychiatric disorders. Common: abnormal behaviour
Nervous system disorders. Common: lethargy
Metabolism and nutrition disorders. Common: decreased appetite

Post-marketing experience
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic system disorders. Agranulocytosis.
Immune system disorders. Drug hypersensitivity reactions. Multiorgan hypersensitivity reactions (also known as drug reaction with eosinophilia and systemic symptoms, DRESS) have been reported in

patients 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. Potential cases have been reported rarely with lacosamide and if multiorgan hypersensitivity reaction is suspected, Vimpat should be discontinued.
Psychiatric disorders. Euphoric mood, suicide attempt and suicidal ideation, aggression, agitation, psychotic disorder, hallucination.
Nervous system disorders. Dyskinesia, seizure. Very few cases of seizure worsening (including occurrence of status epilepticus) have been reported.
Cardiac disorders. Ventricular tachyarrhythmia, Bradycardia, atrioventricular block, atrial fibrillation and atrial flutter.
Hepatobiliary disorders. Liver function test abnormal, hepatic enzyme increased (>2x ULN).
Skin and subcutaneous tissue disorders. Toxic epidermal necrolysis, Stevens-Johnson syndrome, rash, angioedema, urticaria.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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 events 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.

Events reported after an intake of more than 800 mg are dizziness, nausea, 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 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 (see Section 5.2 Pharmacokinetic Properties).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 reduced hyperexcitability of neuronal membranes.

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 trials (partial-onset seizures)

Monotherapy

Efficacy of lacosamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine CR in patients 16 years of age or older with newly or recently diagnosed epilepsy. Patients with idiopathic generalised epilepsy were excluded. The patients were randomized to carbamazepine CR or lacosamide. The dose was based on dose response and ranged from 400 to 1200 mg/day for carbamazepine CR and 200 - 600 mg/day for lacosamide. The duration of the treatment was up to 121 weeks depending on the response.

In the full analysis set (FAS) for the patients with partial-onset seizures, the estimated 6-month seizure freedom rates were 89.5% for lacosamide-treated patients (n=405) and 91.2% for carbamazepine CR treated patients (n=405) using the Kaplan-Meier survival analysis method. The adjusted absolute difference between treatments was -1.8% (95 % CI: -6.1, 2.8). Similar results were observed in the per-protocol set (PPS).

Table 5 – Kaplan-Meier proportion of subjects seizure free for 6 months at the last evaluated dose in the patients with partial-onset seizures

	FAS		**PPS**	
Parameter	LCM N = 405	CBZ-CR N = 405	LCM N = 374	CBZ-CR N = 364
Stratified[a]				
KM seizure free (%) (95% CI)	89.5 (86.3, 92.6)	91.2 (88.2, 94.2)	91.0 (88.0, 94.1)	92.5 (89.5, 95.4)
LCM-CBZ-CR:				
KM seizure free (%) (95% CI)	-1.8 (-6.1, 2.6)		-1.4 (-5.7, 2.8)	
Relative ratio (%)[b]	-6.7		-6.1	

FAS = Full Analysis Set and PPS = Per-Protocol Set.

[a] Estimated by Mantel Haenszel methods.

[b] Relative ratio=Lower limit of 2-sided 95% CI of the stratified difference between LCM and CBZ-CR in seizure-free rates divided by CBZ-CR seizure-free rate

Add-on therapy

The efficacy of Vimpat as add-on therapy in partial-onset seizures was established in three 12 week, randomized, double blind, placebo-controlled, multicenter trials in adult patients. Patients enrolled had partial-onset seizures with or without secondary generalisation and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8 week baseline period, patients were required to have an average of ≥ 4 partial-onset seizures per 28 days with no seizure free period exceeding 21 days. In these 3 trials, patients had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10 to 17 per 28 days. Overall, 84% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation (VNS). In addition, 45% of

patients had taken 7 or more AEDs throughout their lifetime.

Trial SP667 compared doses of Vimpat 200 mg, 400 mg, and 600 mg/day with placebo. Trial SP754 compared doses of Vimpat 400 mg and 600 mg/day with placebo. Trial SP755 compared doses of Vimpat 200 mg and 400 mg/day with placebo. The trials required forced up-titration to the target (randomized) dose over up to 6 weeks (Trial SP667 and Trial SP754) or 4 weeks (Trial SP755). In all 3 trials, active treatment was initiated at 100 mg/day (50 mg given twice daily) and increased in weekly increments of 100 mg/day to the target dose. Subjects randomized to Vimpat 600 mg/day in Trial SP667, Vimpat 400 mg and 600 mg/day in Trial SP754, and Vimpat 400 mg/day in Trial SP755 received active drug beginning at week 1. To facilitate trial blinding, subjects randomized to Vimpat 200 mg and 400 mg/day in Trial SP667 received placebo for the first 4 or 2 weeks, respectively, and subjects randomized to Vimpat 200 mg/day in Trial SP755 received placebo for the first 2 weeks.

In all three trials, following an 8 week baseline phase to establish baseline seizure frequency prior to randomization, subjects were randomized and titrated to the randomized dose (a 1 step back titration of Vimpat 100 mg/day or placebo was allowed in the case of intolerable adverse events at the end of the titration phase). Treatment was maintained for 12 weeks.

A reduction over placebo in seizure frequency per 28 days, the primary variable in all three trials, was significant with Vimpat treatment at doses of 200 mg (Trial SP755, but not Trial SP667), 400 mg (trials SP667, SP754, and SP755), and 600 mg/day (Trials SP667 and SP754). (Table 6, Figure 1.) The 50% responder rates for 400 mg and 600 mg/day Vimpat were also statistically superior to placebo. (Figure 2.)

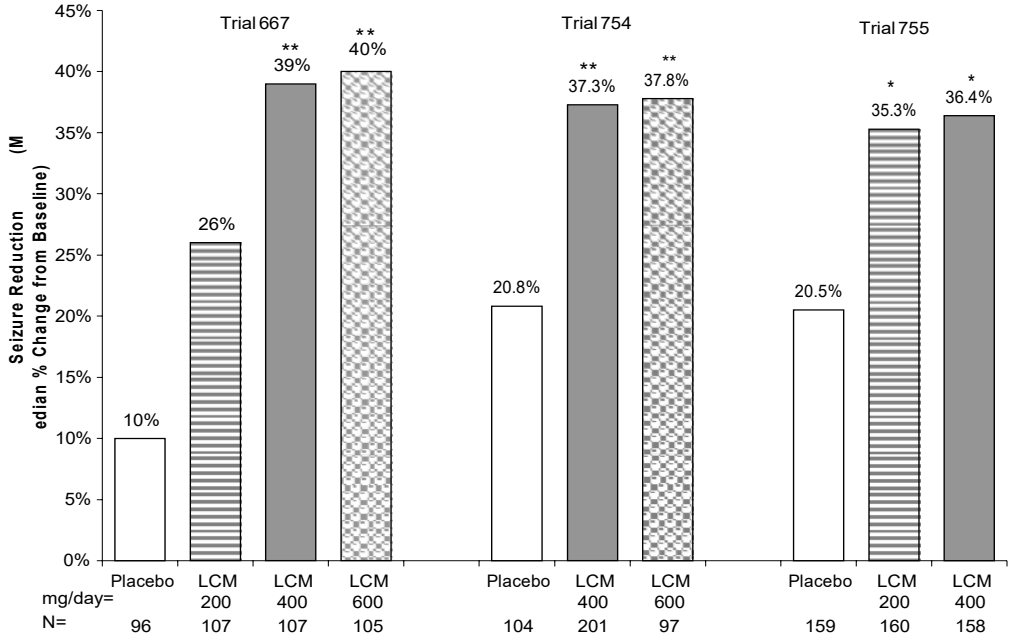
Among the subjects who completed the 12 week maintenance phase, a total across all three trials of 12 (3.3%) and 6 (4.8%) subjects taking Vimpat 400 mg and 600 mg/day, respectively, were seizure free compared with 3 (0.9%) subjects taking placebo.

Table 6 – Vimpat Reduction in Partial-onset Seizure Frequency per 28 Days from Baseline to the Maintenance Phase

Randomized Treatment Group	Number of Patients per Treatment Group	Median Baseline Seizure Frequency per 28 Days	Median Percent Reduction from Baseline	Percent Reduction Over Placebo
Trial SP667				
Placebo	96	11	10%	N/A
200 mg/day	107	13	26%	14.6%
400 mg/day	107	13	39%	28.4%**
600 mg/day	105	11	40%	21.3%**
Trial SP754				
Placebo	104	15	20.8%	N/A
400 mg/day	201	12	37.3%	21.6%**
600 mg/day	97	17	37.8%	24.6%**
Trial SP755				
Placebo	159	10	20.5%	N/A
200 mg/day	160	12	35.3%	14.4%*
400 mg/day	158	10	36.4%	15.0%*

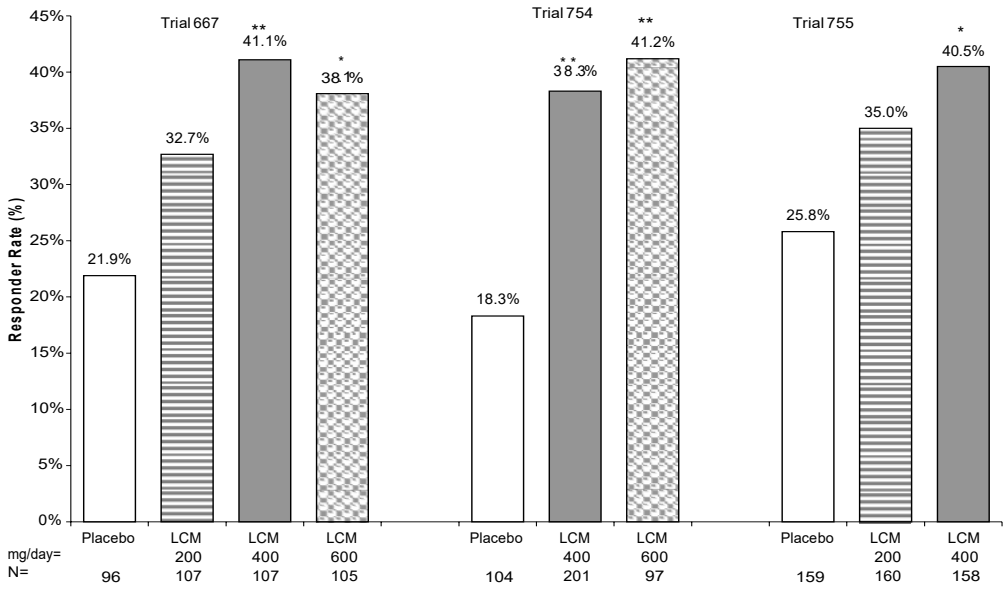
*Significant at the 0.0500 level; **Significant at the 0.0100 level; Percent reduction over placebo and corresponding p-values are based on log-transformed data from pairwise treatment ANCOVA models.
Note: Maintenance Phase includes data for the Titration Phase for patients who discontinued prior to entering the Maintenance Phase.

Figure 1 – Median Percent Reduction in Seizure Frequency per 28 days from Baseline to the Maintenance Phase by Dose



LCM = lacosamide
*Significant at the 0.0500 level; **Significant at the 0.0100 level
p-values are based on log-transformed data from pairwise treatment ANCOVA models

Figure 2 – Responder Rate (≥50% reduction in seizure frequency)



LCM = lacosamide
*Significant at the 0.0500 level; **Significant at the 0.0100 level
p-values are based on pairwise treatment logistic regression models

Note: Responder rate is the proportion of patients with ≥50% reduction in seizure frequency per 28 days from Baseline to the Maintenance Phase

Loading Dose

The pharmacokinetics and safety of a single 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 add-on therapy in adult subjects 16 to 60 years of age with partial-onset seizures.

Paediatric population

In children aged 4 years and older, partial-onset seizures have a similar clinical expression to those in adolescents and adults. The results of efficacy trials performed in adults can be extrapolated to children down to the age of 4 provided the dose is established and safety has been demonstrated. Weight-based dose adaptations have been established to achieve similar plasma concentrations to the ones observed in adults taking efficacious doses.

The extrapolation principle stated above was confirmed in a double-blind, randomized, placebo-controlled study. The study consisted of an 8-week baseline period followed by a 6-week titration period. Eligible patients on a stable dose regimen of 1 to ≤3 AEDs, who still experienced at least 2 partial-onset seizures during the 4 weeks prior to screening with seizure-free phase no longer than 21 days in the 8-week period prior to entry into the baseline period, were randomized to receive either placebo (n=172) or lacosamide (n=171).

Dosing was initiated at a dose of 2 mg/kg/day in subjects weighing less than 50 kg or 100 mg/day in subjects weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 1or 2 mg/kg/day increments in subjects weighing less than 50 kg or 50 or 100

mg/day or 100mg/day in subjects weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose range.

Subjects must have achieved the minimum target dose for their body weight category for the final 3 days of the titration period to be eligible for entry into the 10-week maintenance period. Subjects were to remain on stable lacosamide dose throughout the maintenance period or were withdrawn and entered in the blinded taper period.

Statistically significant (p=0.0003) and clinically relevant reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was observed between the lacosamide and the placebo group. The percent reduction over placebo based on analysis of covariance was 31.72% (95% CI: 16.342,44.277).

Overall, the proportion of subjects with at least a 50% reduction in partial-onset seizure frequency per 28 days from baseline to the maintenance period was 52.9% in the lacosamide group compared with 33.3% in the placebo group.

The quality of life assessed by The Paediatric Quality of Life Inventory (PedsQL) indicated that subjects in both lacosamide and placebo groups had a similar and stable health-related quality of life during the entire treatment period.

Clinical trials (primary generalised tonic-clonic seizures)

The efficacy of lacosamide as add-on therapy in patients 4 years of age and older with idiopathic generalised epilepsy experiencing primary generalised tonic-clonic seizures (PGCTS) was established in a 24-week double-blind, randomized, placebo-controlled, parallel-group, multi-center study. The study consisted of a 12-week historical baseline period, a 4-week prospective baseline period and a 24-week treatment period (which included a 6-week titration period and an 18-week maintenance period). Eligible patients on a stable dose of 1 to 3 antiepileptic drugs experiencing at least 3 documented PGTCS during the 16-week combined baseline period were randomized 1 to 1 to receive lacosamide or placebo (lacosamide n=121, placebo n=121).

Patients were dosed on a fixed-dose regimen. Dosing was initiated at a dose of 2 mg/kg/day in patients weighing less than 50 kg or 100 mg/day in patients weighing 50 kg or more in 2 divided doses. During the titration period, lacosamide doses were adjusted in 2 mg/kg/day increments in patients weighing less than 50 kg or 100 mg/day in patients weighing 50 kg or more at weekly intervals to achieve the target maintenance period dose of 12 mg/kg/day in patients weighing less than 30 kg, 8 mg/kg/day in patients weighing from 30 to less than 50 kg or 400 mg/day in patients weighing 50 kg or more.

The primary efficacy endpoint (patients in the full analysis set: lacosamide n=118, placebo n=121) was time to second PGTCS during the 24-week treatment period. The key secondary endpoint of efficacy was seizure freedom for PGTCS during the 24-week treatment period.

Table 7 – Time to second PGTCS and seizure freedom during 24-week treatment period

Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Time to second PGTCS		
Median (days)	77.0	-
95 % CI	49.0, 128.0	-
Lacosamide – Placebo		
Hazard Ratio	0.540	
95 % CI	0.377, 0.774	
p-value	< 0.001	

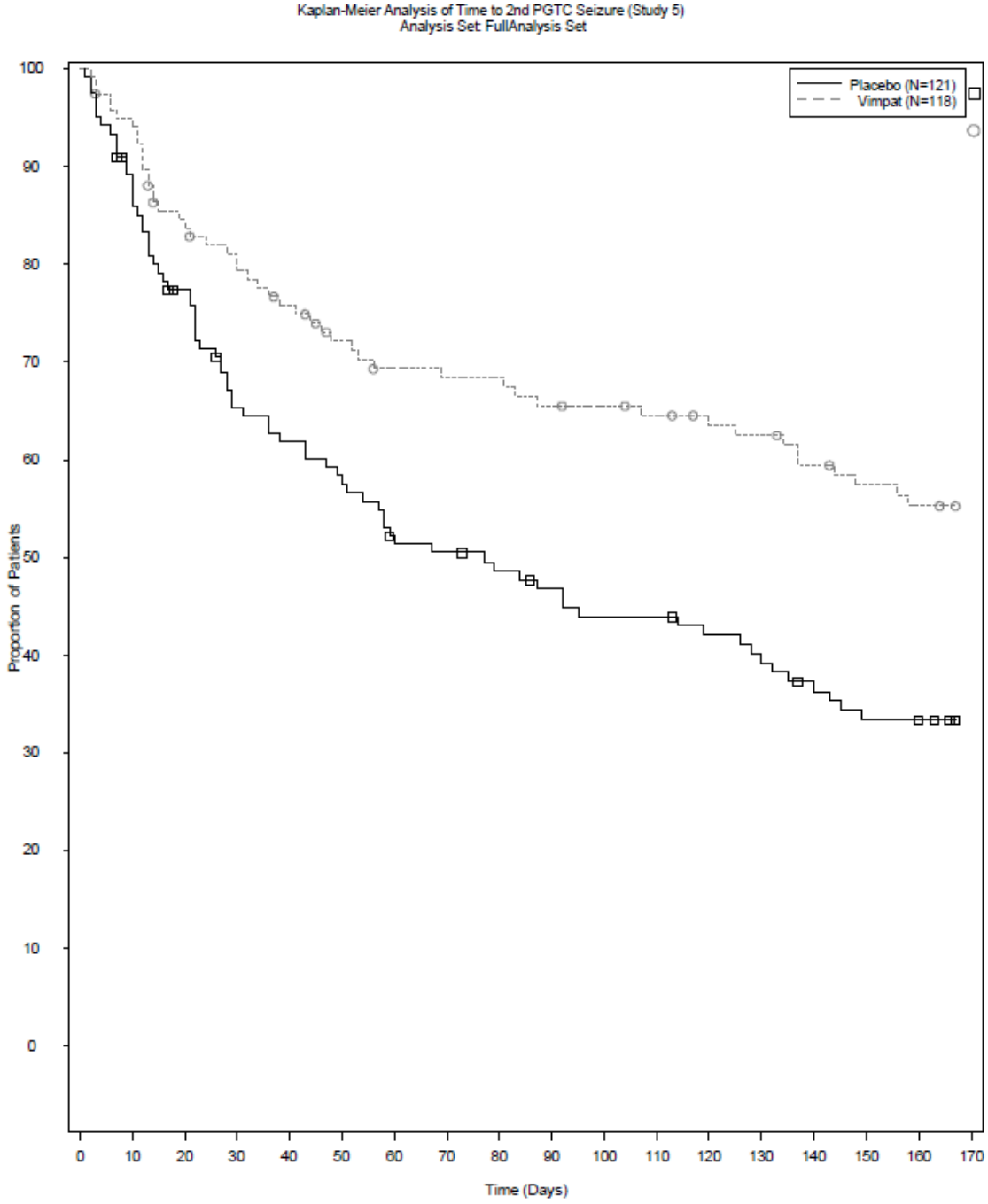
Efficacy variable Parameter	Placebo N=121	Lacosamide N=118
Seizure freedom		
Stratified Kaplan-Meier estimate (%)	17.2	31.3
95 % CI	10.4, 24.0	22.8, 39.9
Lacosamide – Placebo	14.1	
95 % CI	3.2, 25.1	
p-value	0.011	

Note: For the lacosamide group, the median time to second PGTCS could not be estimated by Kaplan-Meier methods because > 50% of patients did not experience a second PGTCS by Day 166.

During the 24-week treatment period, the proportion of patients with at least a 50% reduction in PGTCS frequency per 28 days from baseline to the treatment period was 68.1% in the lacosamide group compared with 46.3% in the placebo group; the proportion of patients with at least a 75% reduction in PGTCS frequency per 28 days from baseline to the treatment period was 57.1% in the lacosamide group compared to 36.4% in the placebo group.

The findings in the paediatric subgroup (20.2% of enrolment) were consistent with the results of the overall population for the primary, secondary and other efficacy endpoints.

Figure 3 – Responder Rate (≥50% reduction in seizure frequency)



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. Lacosamide tablets and oral solution are bioequivalent. Food does not affect the rate and extent of absorption.

After intravenous administration C_{max} is reached at the end of infusion. The plasma concentration

increases proportionally with dose after oral (100 mg-800 mg) and intravenous (50-300 mg) administration.

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

Metabolism
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 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.

CYP2C19, 2C9 and 3A4 are mainly responsible for the formation of the O-desmethyl metabolite, with a minor contributing role by CYP2C19. 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). No other enzymes have been identified to be involved in the metabolism of lacosamide.

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.

Excretion
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 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.

Modelling shows 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 Dose and Method of Administration). 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 nonrenal 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 Dose and Method of Administration).

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 bodyweight. The bodyweight 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 Dose and Method of Administration).

Paediatric population
The paediatric pharmacokinetic profile of lacosamide was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in one placebo-controlled randomized study and three open-label studies in 414 children with epilepsy.

The typical volume of distribution (V/F) was 0.71 L/kg. The typical plasma clearance was estimated to be 1.04 L/h, 1.32 L/h and 1.86 L/h for children weighing 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.92 L/h in adults (70 kg body weight).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Lacosamide was inactive in an *in vitro* mouse L5178Y lymphoma assay (tk locus) with positive or equivocal response only at excessive concentrations of 3 mg/mL (12 mM) and above. No genotoxicity was observed in tests for bacterial gene mutation *in vitro* and unscheduled DNA synthesis in rat hepatocytes *ex vivo,* or in an *in vivo* mouse micronucleus test for clastogenicity.

Carcinogenicity
Lacosamide did not show any tumourigenic responses in long-term carcinogenicity studies in mice and rats. The highest oral doses used resulted in systemic drug exposures (based on plasma AUC_{0-24h}) that were similar to (mice) or about three times (rats) that in humans treated with the maximum recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Vimpat film-coated tablets contain the following inactive ingredients: colloidal anhydrous silica, crospovidone, hyprolose, magnesium stearate, macrogol 3350, microcrystalline cellulose, polyvinyl alcohol, purified talc, titanium dioxide and dye pigments as specified below:

50 mg tablets: Iron oxide red C177491, iron oxide black C177499, indigo carmine C173015.

100 mg tablets: Iron oxide yellow C177492.

150 mg tablets: Iron oxide yellow C177492, iron oxide red C177491, iron oxide black C177499.

200 mg tablets: Indigo carmine C173015.

Vimpat oral solution contains the following inactive ingredients: glycerol, carmellose sodium, sorbitol solution (70 per cent) (crystallising), macrogol 4000, sodium chloride, citric acid, acesulfame potassium, sodium methyl hydroxybenzoate, Strawberry flavor 501440 T (PI#11565), Masking flavor 501521 T (PI# 12943) and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Vimpat film-coated tablets: 4 years.

Vimpat oral solution: 3 years. Once open, discard within 2 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store Vimpat film-coated tablets below 30°C.

Store Vimpat oral solution below 30°C. Do not refrigerate, Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Vimpat film-coated tablets are blister packed and available in strengths of 50 mg, 100 mg, 150 mg, and 200 mg lacosamide.

50 mg: Available in blister packs containing 14, 56* and 168* tablets.

100 mg: Available in blister packs containing 14, 56 and 168* tablets.

150 mg: Available in blister packs containing 14, 56 and 168* tablets.

200 mg: Available in blister packs containing 14*, 56 and 168* tablets.

**not currently distributed in Australia.*

Vimpat oral solution is packed in a 200 mL amber glass bottles with a child resistant closure and is available as 10 mg/mL strength. The pack also contains an oral syringe 10 mL.

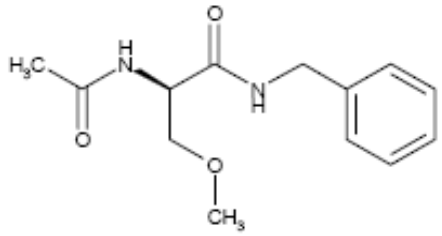
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: (R)-2-acetamido-N-benzyl-3-methoxypropionamide
Molecular formula: $C_{13}H_{18}N_2O_3$
MW: 250.30

Chemical structure



CAS number
175481-36-4

The active ingredient lacosamide is a white to light yellow powder. It is sparingly soluble in water (30 mg/mL at 25°C) and slightly soluble in acetonitrile and ethanol.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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A division of UCB Australia Pty Ltd
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Malvern VIC 3144, Australia
Phone: +613 9828 1800
Website: www.ucbaustralia.com.au
E-mail: medicalinformationAU@ucb.com

9 DATE OF FIRST APPROVAL

31 July 2012

10 DATE OF REVISION

16th May 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Added statement “excretion in human breast milk’