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ADIS DRUG EVALUATION

Lacosamide: A Review of Its Use as Adjunctive Therapy in the Management of Partial-Onset Seizures

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Abstract Lacosamide (Vimpat®) is a functionalized amino acid available orally (as a syrup or tablet) and as an intravenous infusion. It is believed to exert its antiepileptic effect by selectively enhancing the slow inactivation of voltage-gated sodium channels. Lacosamide is approved in several countries worldwide as an adjunctive therapy for the treatment of partial-onset seizures; however, prescribing regulations differ between countries. This article reviews the use of lacosamide as indicated in adults and adolescents (aged 16–18 years) in the EU, where it is approved in this patient population as an adjunctive therapy to other AEDs in the treatment of partial-onset seizures, with or without secondary generalization. In three randomized, double-blind, placebo-controlled, multicentre studies in adults and adolescents (aged 16–18 years) with partial-onset seizures, adjunctive therapy with oral lacosamide (administered for an initial titration period followed by 12 weeks' maintenance therapy) generally reduced the frequency of seizures to a significantly greater extent than placebo, with antiepileptic efficacy sustained following longer-term treatment (up to 8 years) in this patient population. Oral and intravenous lacosamide were generally well tolerated in clinical studies, with the majority of adverse events being mild or moderate in severity. Very common adverse reactions following adjunctive therapy with oral lacosamide included diplopia, dizziness, headache and nausea; the tolerability profile of intravenous lacosamide appeared consistent with that of oral lacosamide, although intravenous administration was associated with local adverse events, such as injection site discomfort or pain, irritation and erythema. Thus, oral and intravenous lacosamide as an adjunctive therapy to other AEDs provides a useful option in the treatment of patients with partial-onset seizures.

Lacosamide as adjunctive therapy in the management of partial-onset seizures: a summary

Selectively enhances the slow inactivation (but has no apparent effect on the fast inactivation) of voltage-gated sodium channels

Available orally (as a syrup or tablet) or as an intravenous infusion, with direct conversion to or from the oral and intravenous formulations achievable without dose adjustment

Reduces seizure frequency in adults and adolescents (aged 16–18 years) with refractory partial seizures

Benefits maintained during longer-term adjunctive therapy

Is generally well tolerated when administered orally or intravenously; very common adverse reactions following adjunctive therapy with oral lacosamide included diplopia, dizziness, headache and nausea

Associated with a dose-related prolongation of the PR interval

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1 Introduction

Epilepsy is a neurological disorder characterized by recurrent abnormal and excessive neuronal discharges in the brain that clinically manifest as seizures [1]. Its clinical presentation is dependent upon, among other factors, the part of the brain affected, the pattern in which the epileptic discharges spread through the brain, the cause of the epilepsy and the age of the individual [1]. Partial seizures originate within networks limited to one hemisphere and may be either localized or more extensively distributed [2]. They represent the most frequent seizure type in adults [1, 3].

Epileptic discharges arise from an imbalance (excitation predominating over inhibition) in the normal excitatory and inhibitory mechanisms that modify neuronal excitability [4, 5]. One such mechanism is voltage-gated sodium channels; on an ionic level, inward calcium or sodium currents mediate excitation [5]. In general, effective seizure therapies oppose excitatory processes or augment inhibitory processes [5]. The inhibition of voltage-gated sodium channels is the principle mechanism of action of several antiepileptic drugs (AEDs) [5], including the functionalized amino acid lacosamide (Vimpat®) [6].

This article reviews the therapeutic efficacy and tolerability of oral and intravenous lacosamide as adjunctive therapy in adults and adolescents with partial-onset seizures, and overviews their pharmacological properties.

2 Pharmacodynamic Properties

The pharmacodynamic properties of lacosamide are well established and have been reviewed previously [7]; therefore, a brief overview is presented in this section.

The exact mechanism of action by which lacosamide exerts its antiepileptic effect is as yet unclear [6, 8]. However, in in vitro electrophysiological studies lacosamide selectively enhanced the slow inactivation of voltage-gated sodium channels, stabilizing hyperexcitable neuronal membranes and inhibiting repetitive neuronal firing [6, 8, 9]. Unlike carbamazepine, lamotrigine and phenytoin, lacosamide has no apparent effect on the fast inactivation of voltage-gated sodium channels [9].

Collapsin response mediator protein-2 (CRMP-2) is a phosphoprotein primarily expressed in the nervous system and involved in neuronal differentiation and the control of axonal outgrowth [8, 10]. Currently, the role of CRMP-2 binding in seizure control is unknown [8], although an in vitro study in hippocampal cells found CRMP-2 to be dysregulated in patients with mesial temporal lobe epilepsy [10]. To date, data regarding the binding affinity of lacosamide for CRMP-2 are equivocal [8, 11]. CRMP-2 has been identified as a regulator of the N-type voltage-gated calcium channel; however, lacosamide does not appear to affect N- or P/Q-type calcium channels in rat hippocampi or L-type calcium channels in murine CNS neurons [12].

In vitro, lacosamide and O-desmethyl lacosamide, the major metabolite of lacosamide (see Sect. 3), do not appear to bind with high affinity (defined as >50 % inhibition of radioligand binding) to a broad range of animal or recombinant human receptor sites, including those for adenosine, benzodiazepine, dopamine, gamma-aminobutyric acid (GABA), histamine, muscarine, NMDA and serotonin 5-HT, or ion channels, including L- and N-type voltage-gated calcium channels and voltage-gated chloride and potassium channels [7, 13, 14]. Moreover, lacosamide does not appear to inhibit GABA transaminase nor the uptake mechanisms of dopamine, GABA, norepinephrine and serotonin 5-HT [13].

Lacosamide has demonstrated antiepileptic activity in a broad range of animal models of partial and primary generalized seizures, and delayed kindling development [6]. In preclinical studies, it has demonstrated synergistic or additive anticonvulsant effects when administered in combination with carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, topiramate or valproate [6, 7, 15].

Limited data suggest that adjunctive lacosamide may exert a positive effect on nocturnal sleep and not affect diurnal vigilance, according to a study in 10 patients with partial-onset seizures who received adjunctive lacosamide 200–400 mg/day for 6 months (compared with 10 matched healthy controls) [16].

Evidence from seven case reports in patients with refractory epilepsy suggest a potential pharmacodynamic interaction between lacosamide and other voltage-gated sodium channel-blocking AEDs (e.g. carbamazepine, lamotrigine, phenytoin), with adverse events (neurotoxicity) alleviated with reductions in the dosages of the concomitant AEDs, although further data are needed [17].

2.1 Effects on Cardiac Parameters

The corrected QT (QTc) interval and the QRS duration do not appear to be affected by therapeutic and supratherapeutic dosages of oral lacosamide, according to a randomized, double-blind study in healthy volunteers ($n = 247$) who received oral lacosamide 400 or 800 mg/day, placebo or a positive control (moxifloxacin 400 mg) [8]. However, lacosamide is associated with small, dose-dependent elevations in the PR interval [7, 8]. In the study in healthy volunteers [8], the time of the maximum

observed mean PR interval at steady state corresponded with the time to the maximum concentration (C_{max}), with a placebo-subtracted maximum increase in PR interval (at the time to C_{max}) of 7.3 ms for the lacosamide 400 mg/day group and 11.9 ms for the lacosamide 800 mg/day group. The increases in the mean PR interval observed in patients with partial-onset seizures participating in the three double-blind, multicentre studies [18–20] (discussed in Sect. 4) are presented in Sect. 5.1.1.

In addition to the data described with single-agent lacosamide, data from subgroup analyses of clinical studies found no increase in the magnitude of PR interval prolongation in patients receiving concomitant therapy with lacosamide and carbamazepine or lamotrigine [6]. However, caution is advised with the coadministration of lacosamide and agents known to be associated with PR prolongation (e.g. carbamazepine, lamotrigine, pregabalin) [see Sect. 7] or class I antiarrhythmic agents [6].

3 Pharmacokinetic Properties

The pharmacokinetic properties of lacosamide have been discussed in detail previously [7]; this section provides a brief summary.

In the EU, lacosamide is available as 50, 100, 150 and 200 mg tablets, a 10 mg/mL syrup and a 10 mg/mL solution for infusion [6]. Bioequivalence between two 100 mg tablets and a 30- and 60-minute infusion of lacosamide 200 mg [21] and between two 100 mg tablets and 20 mL of a lacosamide 10 mg/mL syrup formulation (total dose 200 mg) [22] was demonstrated in healthy male volunteers aged 18–45 years participating in two randomized, nonblind, crossover studies ($n = 27$ [21] and 16 [22]). The 90 % confidence intervals for the ratios of the area under the concentration-time curve (AUC) from 0 h to the last quantifiable plasma concentration (AUC_{tz}) and plasma C_{max} were within the European Medicines Agency limits of 0.80 to 1.25 [21, 22]. However, bioequivalence between two 100 mg tablets and a 15-minute infusion of lacosamide 200 mg was not demonstrated in a randomized, nonblind, crossover study in healthy male volunteers ($n = 16$) aged 18–45 years, as the 90 % confidence interval for the plasma C_{max} ratio exceeded the upper boundary limit of 1.25 [21]. The 90 % confidence interval for the AUC_{tz} ratio was within the European Medicines Agency limits of 0.80 to 1.25 [21].

Lacosamide exhibits dose-proportional pharmacokinetics in the 100–800 mg dose range that have low inter- and intra-subject variability and are constant over time [6, 8]. Exposure of lacosamide was correlated with a reduction in seizure frequency, according to a pharmacokinetic-pharmacodynamic analysis [8] utilizing pooled data from three double-blind, multicentre studies in adults and adolescents (aged 16–18 years) with partial-onset seizures (discussed in Sect. 4) [18–20]. However, according to group analyses, dosages >400 mg/day do not appear to confer any additional benefit [8]. A retrospective study in 70 patients with poorly controlled epilepsy receiving adjunctive lacosamide suggests that there is no correlation between serum concentrations and weight-dependent dosages of lacosamide and clinical tolerability [23].

Following oral administration, lacosamide is rapidly and completely absorbed from the gastrointestinal tract; the oral bioavailability of the tablet formulation is approximately 100 % (owing to a negligible first-pass effect) [6, 8]. The rate and extent of absorption is not affected by food (see Sect. 7) [6, 8]. The C_{max} of unchanged lacosamide was reached 0.5–4 h post dose following oral administration [6, 22] and at the end of the infusion following intravenous administration [8, 21]. The plasma concentration of lacosamide increases with an accumulation factor of approximately 2, with steady-state plasma concentrations achieved after a 3-day period of twice-daily dosing [6, 8]. A single loading dose of 200 mg approximates steady-state concentrations comparable to oral lacosamide 100 mg twice daily [6].

The volume of distribution of lacosamide is approximately 0.6 L/kg [6, 8] and, therefore, close to the total body water volume [8]. Less than 15 % of lacosamide is bound to plasma proteins [6, 8].

The pathway for the metabolism of lacosamide has not been completely characterized [6]. Although in vitro studies have shown that cytochrome P450 (CYP) 2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of O-desmethyl lacosamide (see Sect. 3.2), the major contributing isoenzyme has not been confirmed in vivo. No clinically relevant difference in lacosamide exposure was observed in extensive metabolizers (i.e. patients with a functional CYP2C19) compared with poor metabolizers (i.e. patients lacking a functional CYP2C19), indicating that this pathway is of minor importance [6]. Furthermore, no clinically relevant changes in the plasma concentration of lacosamide were observed when lacosamide was administered concurrently with the CYP2C19 inhibitor omeprazole [6]. The plasma concentration of O-desmethyl lacosamide, which has no known pharmacological activity, is approximately 15 % that of lacosamide [6]; the time to the C_{max} of O-desmethyl lacosamide is 0.5–12 h [8].

Lacosamide is predominately eliminated from the systemic circulation via renal excretion and biotransformation [6, 8]. The elimination of lacosamide occurs primarily via the urine (97 and 94 % for intravenously and orally administered lacosamide, respectively); negligible amounts (<0.5 %) are recovered in faeces [24]. Unchanged

lacosamide (38 and 34 % for intravenously and orally administered lacosamide, respectively), its O-desmethyl metabolite (28 and 28 %) and a structurally unknown polar fraction (possibly serine derivatives [6]; 19 and 17 %) are the major compounds present in the urine [24].

The elimination half-life of lacosamide is approximately 13 h [6, 8] and is not altered by different doses, multiple dosing or intravenous administration [8]. The elimination half-life of O-desmethyl lacosamide is 15–23 h [8].

3.1 Special Populations

In the EU [6], dosage adjustments are not required in elderly patients unless indicated because of reduced renal function, with the plasma concentration of lacosamide not affected to a clinically significant extent by gender. According to the US prescribing information, there are no clinically relevant differences in the pharmacokinetics of lacosamide between Asian, Black and Caucasian subjects [8].

Compared with healthy subjects, lacosamide AUC_{tz} values were elevated by approximately 25 % in patients with mild (creatinine clearance [CL_{CR}] ≥50 to <80 mL/min) or moderate (CL_{CR} ≥30 to <50 mL/min) renal impairment following the oral administration of a single dose of lacosamide 100 mg [25]. Therefore, according to the EU summary of product characteristics (SPC) [6], dosage adjustments are not required in this patient population, nor in patients with mild to moderate hepatic impairment; a loading dose of 200 mg may be considered, although further dose titration (>200 mg/day) should be exercised with caution. Data are lacking in patients with severe hepatic impairment [6].

Lacosamide AUC_{tz} values were elevated by approximately 60 % in patients with severe renal impairment (CL_{CR} ≥15 to <30 mL/min) or those with endstage renal disease requiring haemodialysis (CL_{CR} <15 mL/min), compared with those in healthy subjects, following the oral administration of a single dose of lacosamide 100 mg [25]. Therefore, in the EU, a maximum maintenance dosage of 250 mg/day and cautious dose titration is recommended in these patient populations [6]. For patients requiring a loading dose, an initial dose of 100 mg followed by a 50 mg twice-daily (100 mg/day) maintenance regimen for the first week should be used. Although the O-desmethyl metabolite has no known pharmacological activity, it is as yet unknown whether its accumulation in patients with end-stage renal disease may result in adverse events. In light of this and the limited clinical experience in this patient population, patients with end-stage renal disease should be treated with caution. Lacosamide is eliminated from the plasma by haemodialysis [6], with the mean AUC from 0 to 24 h of lacosamide reduced by approximately 50 % following haemodialysis of 4 hours' duration [6, 25]. Therefore, dosage supplementation of up to 50 % of the divided daily dose of lacosamide is recommended directly after the end of haemodialysis [6].

3.2 Potential Drug Interactions

Data from in vitro studies indicate that lacosamide does not induce CYP1A2, CYP2B6 and CYP2C9 or inhibit CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP2E1, with neither CYP2C19 nor CYP3A4 induced or inhibited to a clinically relevant extent by lacosamide in vivo [6]. Concurrent therapy with lacosamide 300 mg twice daily and omeprazole 40 mg once daily (a CYP2C19 inhibitor) had no effect on the pharmacokinetics of omeprazole and no clinically significant effect on the exposure of lacosamide, with moderate CYP2C19 inhibitors considered unlikely to affect the systemic exposure of lacosamide to a clinically significant extent. However, the EU SPC [6] advises caution with the coadministration of lacosamide and strong CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. clarithromycin, ketoconazole, ritonavir) inhibitors, as concurrent therapy may increase the systemic exposure of lacosamide, and with the commencement and cessation of treatment with strong enzyme inducers such as rifampicin (rifampin) and hypericum (St. John's wort), as they may moderately reduce the systemic exposure of lacosamide.

An in vitro study has demonstrated that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of O-desmethyl lacosamide [6], with plasma concentrations of the O-desmethyl metabolite reduced by approximately 60 % following the coadministration of a single dose of lacosamide 300 mg and omeprazole 40 mg twice daily (patient population not reported) [8].

A population pharmacokinetic analysis demonstrated a 25 % reduction in the overall systemic exposure of lacosamide following concomitant therapy (at various doses) with other AEDs known to be enzymes inducers (e.g. carbamazepine, phenobarbital, phenytoin) [6]. However, there were no clinically relevant pharmacokinetic interactions observed between lacosamide and carbamazepine sustained release [26] or valproic acid [27] in healthy volunteers, with no effect on the steady-state plasma concentrations of various AEDs observed following coadministration with lacosamide in patients with partial onset-seizures [8].

Lacosamide does not affect the pharmacokinetics of digoxin [6, 8], metformin [6, 8], midazolam [28] or warfarin [29], according to studies in healthy volunteers. Furthermore, there are no clinically relevant effects of lacosamide on ethinylestradiol and levonorgestrel, nor on the concentrations of progesterone in healthy volunteers [30].

As lacosamide is minimally (<15 %) protein bound [31], clinically relevant interactions with other agents via competition for protein binding sites are considered unlikely [6, 8].

According to the US prescribing information [8], lacosamide is neither an inhibitor nor a substrate of p-glycoprotein (p-gp) [as its efflux ratio is less than 2 [32]], with an in vitro study reported in the EU SPC [6] demonstrating that lacosamide is not transported by p-gp in the intestine. Recent evidence suggests p-gp may play a role in the overall disposition of lacosamide, with an in vitro study [32] demonstrating the transportation of a clinically relevant concentration of lacosamide (5 μg/mL) by p-gp (MDR1) from the basolateral to the apical side of LLC-MDR1 and MDCK-MDR1 cells. Transportation was blocked by the p-gp inhibitors tariquidar and verapamil; no transportation was observed in wild-type cells. However, in the same study, lacosamide demonstrated high permeability (in both directions) in Caco-2 cells, with efflux ratios of <1.5, and did not inhibit the p-gp substrate digoxin [32]. Further studies are warranted.

4 Therapeutic Efficacy

The therapeutic efficacy of oral lacosamide as an adjunct to other AEDs was evaluated in adults [18–20] and adolescents (aged 16–18 years) [19, 20] with partial-onset seizures in three randomized, double-blind, placebo-controlled, multicentre, phase II [18] or III [19, 20] studies of 16 [20] and 18 [18, 19] weeks' treatment duration (Studies SP667 [18], SP754 [19] and SP755 [20]) [Sect. 4.1]. The longer-term efficacy of lacosamide has been assessed in three noncomparative extension studies (Studies SP615 [33], SP756 [34] and SP774 [35]) and a double-blind, double-dummy, multicentre phase II study [36] (Sect. 4.2), which primarily evaluated tolerability endpoints (Sect. 5). Data from pooled analyses [37–43] (Sect. 4.3) and noncomparative, observational and retrospective studies [44–52] (Sect. 4.4) are also discussed. Some data are from abstracts [33, 35, 38, 40–46, 48, 52, 53], with limited supplementary data from a recent review [54], ClinicalTrials.gov [55], data on file [56] and the EU assessment report [57]. Discussion focuses on data for lacosamide 200 and 400 mg/day, which are the maintenance dosages approved in the EU. Although two [18, 19] of the three studies also investigated the efficacy of adjunctive lacosamide 600 mg/day, the use of this dosage is not recommended as its efficacy was similar to that observed with the 400 mg/day dosage and it was less likely to be tolerated owing to CNS- and gastrointestinal-related adverse events [6]. Unless otherwise stated, lacosamide was administered orally.

4.1 Phase II/III Studies

The studies utilized similar inclusion and exclusion criteria, with patients aged 16–70 [19, 20] or 18–65 [18] years with a diagnosis of simple or complex partial-onset seizures (based on the 1981 International League Against Epilepsy Classification of Epileptic Seizures [58]), with or without secondary generalization, and a history of partial-onset seizures for at least the previous 2 years despite prior therapy with ≥2 AEDs eligible for enrolment [18–20]. Patients were also required to have experienced (an average of [18, 20]) at least four partial-onset seizures per 28 days, with a seizure-free period of no longer than 21 days, in the 8 [18] or 16 [19, 20] weeks prior to randomization and to be receiving stable dosage regimens of at least one [18–20], but no more than two [18] or three [19, 20] AEDs, with or without vagus nerve stimulation, in the 12 weeks prior to randomization. Nonepileptic or psychogenic seizures and a history of chronic alcohol or drug abuse [19, 20] within the previous 2 years [18], primary generalized seizures, status epilepticus in the last 12 months and severe anaphylactic reaction or serious blood dyscrasias were among the exclusion criteria [18–20].

Following an 8-week baseline period, eligible patients were randomized to receive lacosamide (administered as two equally divided doses) or placebo as an adjunct to AED therapy, with the target dosage of lacosamide (200 [18, 20], 400 [18–20] or 600 [18, 19] mg/day) achieved during a 4- [20] or 6-week [18, 19] titration period (in which the 100 mg/day starting dosage was increased by 100 mg/day each week) and then maintained throughout a 12-week maintenance period [18–20]. At the end of the titration period, patients experiencing an intolerable adverse event were permitted one down-titration (of 100 mg/day) in the dosage of lacosamide; the reduced dosage was then continued during the maintenance period, with patients requiring a second down-titration discontinued from the study [18–20]. Following completion of the maintenance period, patients could enter a noncomparative extension study, subsequent to a 2-week blinded transition period [18–20], or discontinue the study medication over 2 [20] or 3 weeks [18, 19].

The primary efficacy endpoints were based on the change in seizure frequency, as assessed from patients' diaries, and included the change from baseline to the end of the maintenance period in seizure frequency per 28 days and the proportion of patients with a ≥50 % reduction in the frequency of partial-onset seizures (i.e. responders) [per 28 days [20]] relative to baseline [18–20]. The respective endpoints are in line with US FDA and European regulatory agencies' requirements [57].

At baseline, patient demographic and disease characteristics were comparable between the lacosamide and

placebo treatment groups [18–20]. According to a pooled analysis, the median seizure frequency per 28 days during the baseline period was 12.2, 11.0 and 11.0 in patients randomized to the lacosamide 200 mg/day ($n = 267$) and 400 mg/day ($n = 466$), and placebo ($n = 359$) groups, respectively (intent-to-treat [ITT] population) [37]. In the respective groups, 88, 83 and 83 % of patients were receiving two or three AEDs (including carbamazepine, lamotrigine, levetiracetam, topiramate and/or valproate), with 45, 44 and 45 %, respectively, treated with at least seven AEDs over their lifetime [37]. Where reported, 25.4 % (51 of 201 patients) of lacosamide 400 mg/day recipients and 37.5 % (39 of 104) of placebo recipients from Study SP754 [19] and 7.5 % (12 of 160) of lacosamide 200 mg/day recipients, 7.0 % (11 of 158) of lacosamide 400 mg/day recipients and 8.8 % (14 of 159) of placebo recipients from SP755 [20] were utilizing vagus nerve stimulation. Efficacy analyses were conducted in the ITT population and the per-protocol population (see Table 1 for definitions) [18–20].

For the most part, adjunctive therapy with lacosamide was effective in the treatment of adults and adolescents (aged 16–18 years) with partial-onset seizures. Compared with placebo, lacosamide 400 mg/day was associated with significantly greater improvements in both seizure frequency per 28 days and the proportion of patients achieving a ≥50 % change from baseline in seizure frequency in the ITT populations of all three studies [18–20], whereas lacosamide 200 mg/day was not consistently associated with significantly greater improvements in these endpoints in the two studies that evaluated this dosage [18, 20] (Table 1). In the per-protocol analyses of these endpoints, between-group differences significantly favoured lacosamide 400 mg/day versus placebo for all comparisons and lacosamide 200 mg/day versus placebo in all but one comparison (Table 1).

In Study SP754 [19], adjunctive therapy with lacosamide 400 mg/day resulted in median percentage changes from baseline to the end of the maintenance period in the frequency per 28 days of simple partial seizures, complex partial seizures and secondarily tonic-clonic seizures of −34.9, −38.7 and −59.4 %, respectively; corresponding values following placebo were −47.6, −22.2 and −14.3 % (ITT population) [no statistical analysis reported]. The proportion of responders for simple partial seizures, complex partial seizures and secondarily tonic-clonic seizures were 38.4, 40.0 and 56.0 %, respectively, in the lacosamide 400 mg/day group and 43.9, 24.4 and 33.3 %, respectively, in the placebo group (ITT population) [19].

Table 1 Efficacy of oral lacosamide, as adjunctive therapy to other antiepileptic drugs, in adults and adolescents (aged 16–18 years) with partial-onset seizures. Summary of double-blind, multicentre studies of 16 [20] and 18 [18, 19] weeks' duration

Study	Treatment[a] (mg/day)	No. of ITT/PP pts	Median change from baseline in seizure frequency per 28 days[b] (%)		Responder rate[c,d] (% of pts)	
			ITT population	PP population	ITT population	PP population
Study SP667 [18][e]	LCM 200	107/NR	−26	−33*	32.7	38.1*
	LCM 400	107/NR	−39***	−46**	41.1***	49.4****
	PL	96/NR	−10	−12	21.9	21.2
Study SP754 [19]	LCM 400	201/NR	−37.3**	−39.6*	38.3****[f]	40.0***
	PL	104/NR	−20.8	−21.7	18.3	18.4
Study SP755 [20]	LCM 200	160/140	−35.3*	−35.3*	35.0	35.0
	LCM 400	158/121	−36.4*	−44.9**	40.5**	46.3**
	PL	159/138	−20.5	−25.4	25.8	27.5

Analyses were conducted in the ITT population (defined as all patients who had received ≥1 dose of the study medication and had ≥1 post-baseline efficacy assessment), with titration period efficacy data carried forward if the patient discontinued therapy prior to commencing the maintenance period, and the PP population (defined as all patients in the ITT population who had ≥1 efficacy assessment during the maintenance period and who did not have any major protocol violations). See text for further dosage and study design details

LCM lacosamide, *ITT* intent-to-treat, NR not reported, *PL* placebo, *PP* per-protocol, *pts* patients

* $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.005$, **** $p < 0.001$ vs. PL

[a] Discussion focuses on data for lacosamide 200 and 400 mg/day, which are the maintenance dosages approved in the EU

[b] Primary efficacy endpoint for the US FDA [57]

[c] Primary efficacy endpoint for the European regulatory agencies [57]

[d] Proportion of pts achieving a ≥50 % improvement from baseline in the frequency of partial-onset seizures

[e] Limited supplementary data from Study SP667 were obtained from a recent review [54]

[f] Odds ratio vs. PL 2.8

The proportion of patients achieving a ≥75 % reduction from baseline to the end of the maintenance period in seizure frequency was significantly higher with lacosamide 400 mg/day than with placebo in the two studies that reported this endpoint (22.4 vs. 6.3 % of patients, $p = 0.002$ [patient population not reported] [18]; 20.4 vs. 7.7 %, $p = 0.005$ [ITT population] [19]). However, no significant difference between lacosamide 200 mg/day and placebo for this endpoint was observed in Study SP667 (patient population not reported) [18].

Throughout the 12-week maintenance periods of Studies SP667 (patient population not reported) [18] and SP754 ($n = 317$ evaluable for the seizure freedom analysis) [19], seizure freedom was observed in five [18] and four [19] lacosamide 400 mg/day recipients and one [18] lacosamide 200 mg/day recipient; no placebo recipient achieved seizure freedom [18, 19]. Among patients completing the maintenance period of Study SP755 ($n = 403$), seizure freedom throughout the 12-week maintenance period was observed in three lacosamide 400 mg/day recipients, five lacosamide 200 mg/day recipients and three placebo recipients [20]. Seizure freedom was also demonstrated in the ITT population of Study SP754 (2 % [4/201] of lacosamide 400 mg/day recipients and 0 % [0/104] placebo recipients) [19].

At the end of the maintenance period of Study SP667 (patient population not reported), there was a statistically significant ($p = 0.0036$) difference in the median change from baseline in the percentage of seizure-free days following therapy with lacosamide 400 mg/day, but not lacosamide 200 mg/day, versus placebo (12 and 6 vs. 3 % of patients) [18]. During the maintenance periods of Studies SP754 [19] and SP755 [20], there was a significant ($p < 0.05$) increase (of ~5 %) over placebo ($n = 98$ [19] and 143 [20]) in the percentage of seizure-free days following therapy with lacosamide 400 mg/day ($n = 168$ [19] and 123 [20]).

Elevations in seizure frequency of ≥25 % were observed in 21 % of patients receiving lacosamide 400 mg/day, 15 % of those receiving lacosamide 200 mg/day and 20 % of those receiving placebo in Study SP667 [18] (no statistical analysis or patient population reported).

In Study SP667 [18], the median change from baseline in the Quality of Life in Epilepsy (QOLIE)-31 scale (scores range from 0 to 100) total score was +2.7 points in the lacosamide 400 mg/day group and −1.3 points in the placebo group (no statistical analysis or patient population reported). An improvement (defined as 'very much improved' or 'much improved') from baseline to the end of the maintenance period was observed in 40 % of lacosamide 400 mg/day recipients, 35 % of lacosamide 200 mg/day recipients and 25 % of placebo recipients (no statistical analysis reported) [18].

4.2 Extensions of Phase II/III Studies

Patients who completed Study SP667 [18] or one of two nonblind phase II studies ($n = 66$ and 2) [the results of which are not discussed] were eligible to enter an extension study (Study SP615) of up to 8 years ($n = 369$) [33, 56]. Patients who completed Study SP754 [19] and Study SP755 [20] were eligible to enter an extension study of up to 5 (Study SP756; $n = 307$) [34] or 5.5 years (Study SP774; $n = 376$) [35].

During a 2-week blinded period following completion of Studies SP667 [18], SP754 [19] and SP755 [20] patients were transitioned from their maintenance dosage to lacosamide 200 mg/day (administered as two equally divided doses), after which the dosage could be modified based on efficacy and tolerability (to a minimum dosage of 100 mg/day and a maximum dosage of 800 mg/day) [33–35]. Concomitant AEDs were adjusted to optimize efficacy and tolerability [33–35]. The median modal dose of lacosamide was 400 mg/day [33, 35] or 500 mg/day [34]; 79.5 % (245 of 308 patients) of patients in Study SP756 received lacosamide modal doses of ≥400 mg/day [34]. The median duration of therapy with lacosamide in Study SP756 was 1,075 days [34].

The antiepileptic efficacy of adjunctive lacosamide was sustained in the longer-term (up to 8 years) treatment of adults and adolescents (aged 16–18 years) with partial-onset seizures [33–35]. For instance, in Study SP774 [35, 55], the median percentage change from baseline (of the double-blind core study) to the end of the treatment period in seizure frequency per 28 days was −49.9 %. Among patients who completed therapy for at least 1 ($n = 279$) or 3 years ($n = 200$), the median percentage changes from baseline in seizure frequency per 28 days were −55.4 and −62.3 %, respectively [35]. Moreover, 50.0 % of patients achieved a ≥50 % reduction from baseline in seizure frequency [35, 55], with a responder rate of 55.9 and 63.0 % among patients who completed therapy for at least 1 or 3 years, respectively [35]. Of those patients exposed to lacosamide therapy for at least 1 year, 3.2 % remained seizure-free for at least 1 year [35].

Significant (p-value not reported) mean improvements in all Seizure Severity Questionnaire (SSQ) subscale scores, including cognitive, emotional and physical effects during and after seizures, and significant (p-value not reported) improvements in the QOLIE-31 total score and all QOLIE-31 subscale scores, apart from medication effects, were observed with lacosamide at week 48, according to a subgroup of patients ($n = 270$) [53] from Study SP756 [34]. Moreover, over 35 % of patients demonstrated clinically meaningful improvements in all QOLIE-31 subscales, with the largest improvements (approximately 50 %) observed for the seizure worry and

social functioning subscales. In terms of the Patient Global Impression of Change, 79.5 % of patients reported an overall improvement at week 16 ($n = 283$), with 53.0 % of patients 'very much improved' or 'much improved'. At week 48 ($n = 244$), 79.1 % of patients reported an overall improvement, with 64.3 % of patients 'very much improved' or 'much improved' [53].

In a double-blind, double-dummy, multicentre study, 60 adults with partial-onset seizures who were currently receiving adjunctive oral lacosamide therapy (as part of an extension study) were randomized to receive oral lacosamide plus placebo or intravenous lacosamide (infused over 30 or 60 min) plus placebo twice daily for 2 days [36]. The intravenous lacosamide dosage (200–600 mg/day) administered was the same as the oral lacosamide dosage previously received by the patients in the extension study. The pattern and daily frequency of seizures experienced with intravenously administered lacosamide among those patients who had a seizure during the treatment period was generally consistent with that experienced prior to study entry (i.e. while receiving orally administered lacosamide) [36].

4.3 Pooled Analyses

In general, the efficacy profile of lacosamide in the pooled analysis [37] of three double-blind, multicentre studies [18–20] in adults and adolescents (aged 16–18 years) with partial-onset seizures was consistent with that observed in the individual studies. A significant median percentage change from baseline to the end of the maintenance period in seizure frequency per 28 days favoured lacosamide 200 ($n = 267$) and 400 mg/day ($n = 466$) over placebo ($n = 359$) in the ITT population (−33.3 and −36.8 vs. −18.4 %; $p < 0.05$ and <0.001) [37]. Significant differences also favoured lacosamide 200 and 400 mg/day over placebo in the proportion of patients achieving a ≥50 % reduction in partial-onset seizure frequency per 28 days (34.1 and 39.7 vs. 22.6 %; $p < 0.05$ and <0.001) [37]. Seizure freedom throughout the maintenance period was observed in 2.2 % of lacosamide 200 mg/day recipients, 2.6 % of lacosamide 400 mg/day recipients and 0.8 % of placebo recipients (ITT population) [37]. In a post hoc analysis of pooled data from all dosage groups of the three double-blind, multicentre studies, there were significant differences observed between patients receiving lacosamide 200–600 mg/day ($n = 935$) and those receiving placebo ($n = 359$) in the mean percentage of seizure-free days over both the entire treatment period (4–6-week titration period plus the 12-week maintenance period) [$p < 0.001$] and at each week ($p \leq 0.020$) [38].

According to a post hoc analysis of pooled data, lacosamide 400 mg/day demonstrated efficacy regardless of the concomitant AEDs used, with a ≥50 % reduction from baseline to the end of the maintenance period in seizure frequency achieved by 37–48 and 14–29 % of patients receiving lacosamide 400 mg/day or placebo as an adjunct to first-generation AEDs and by 30–43 and 18–26 % of patients receiving lacosamide 400 mg/day or placebo as an adjunct to second-generation AEDs [37]. Moreover, in a post hoc subgroup analysis of pooled data from the three double-blind, multicentre studies, the efficacy of adjunctive lacosamide did not appear to be affected by a concomitant AED regimen that includes at least one sodium channel-blocking agent [39]. In patients receiving at least one sodium channel-blocking agent, adjunctive therapy with lacosamide 200 ($n = 201$) and 400 mg/day ($n = 316$) resulted in a significant ($p < 0.01$) median percentage change from baseline to the end of the maintenance period in seizure frequency per 28 days compared with placebo ($n = 273$) [−33.3 and −39.0 vs. −18.9 %]. Corresponding values in lacosamide 200 ($n = 43$) and 400 mg/day ($n = 77$) and placebo ($n = 64$) recipients receiving no sodium-channel-blocking agents were −38.0, −62.5 and −28.0 % ($p < 0.01$ for lacosamide 400 mg/day vs. placebo). Significant ($p < 0.01$) differences in the proportion of responders were also observed for lacosamide 400 mg/day, but not 200 mg/day, versus placebo in patients receiving a concomitant AED regimen containing at least one sodium channel-blocking agent (39.9 and 33.3 vs. 22.7 %) and in patients receiving a concomitant AED regimen containing no sodium channel-blocking agents (62.3 and 41.9 vs. 25.0 %) [39].

In patients receiving lacosamide, significantly ($p < 0.05$) greater improvements in all QOLIE-31 ($n = 738$) and SSQ ($n = 571$) scores were seen in responders than non-responders, according to a post hoc analysis [40, 41].

Longer-term adjunctive therapy with lacosamide was associated with sustained efficacy, according to a subgroup analysis of pooled data from patients in the extension studies who had been exposed only to lacosamide ≤400 mg/day ($n = 363$) [42]. The median percentage change from baseline at 1, 2, 3, 4 and 5 years in seizure frequency per 28 days was −59.4, −64.1, −67.9, −69.3 and −71.0 % among patients who completed therapy for at least 1 ($n = 233$), 2 ($n = 182$), 3 ($n = 149$), 4 ($n = 124$) or 5 ($n = 57$) years, respectively; the proportions of responders among patients who completed therapy for at least 1, 2, 3, 4 or 5 years were 60.2, 65.9, 68.0, 72.6 and 70.2 %, respectively [42].

Following 48 weeks' adjunctive lacosamide therapy, patients exhibited a statistically significant mean improvement in all SSQ subscales, according to a pooled analysis ($n = 607$) [43] of data from all dosage groups from two of the extension studies [34, 35]. Further analyses

including pooled data from all three extension studies ($n = 867$) found statistically significant improvements in the SSQ total score and in the seizure worry and social functioning subscale scores. Moreover, over one-third of patients demonstrated clinically meaningful improvements in all QOLIE-31 subscale scores. Mean improvements in both QOLIE-31 and SSQ remained stable for up to 5 years of therapy [43].

4.4 Observational and Retrospective Studies

In general, therapy with adjunctive lacosamide was effective in the treatment of patients with partial-onset seizures in a real world setting [44–52], supporting data from patients in the double-blind, placebo-controlled, multicentre studies (Sect. 4.1) and their longer-term extensions (Sect. 4.2). Reductions in seizure frequency were reported across three observational studies ($n = 131$ [44], 127 [45] and 99 [46]). For instance, in Stefan et al. [44], adjunctive lacosamide (mean dosage of 296 mg/day) for at least 6 months resulted in a responder rate of 40 %; 8 % of patients were seizure free.

The longer-term efficacy of adjunctive lacosamide in the clinical practice setting was also demonstrated in observational studies in patients with partial-onset seizures ($n = 153$ [47] and 107 [48]). For instance, in Villanueva et al. [47], 46.8 % of patients achieved a ≥50 % reduction from baseline in seizure frequency (co-primary efficacy endpoint) after 12 months' therapy with adjunctive lacosamide (initiated at 50 mg once daily or 100 mg twice daily and titrated to a maximum of 400 mg/day). At this timepoint, 24.1 % of patients were observed to be seizure free (co-primary efficacy endpoint). Among the 153 patients receiving a concomitant AED upon commencing adjunctive therapy with lacosamide, a significantly higher number of those receiving no sodium channel-blocking agent ($n = 49$) versus those receiving at least one sodium channel-blocking agent ($n = 104$) were seizure-free (34.7 vs. 17.3 % of patients; $p = 0.017$) and responded to therapy (65.3 vs. 37.5 %; $p = 0.001$). Moreover, a significantly lower number of concomitant AEDs were being used at the end of the study versus baseline ($p < 0.001$) [47].

Furthermore, the retention of adjunctive lacosamide in patients undergoing long-term treatment (up to 3 years) was demonstrated in another observational study ($n = 376$), in which patients with mainly medically refractory epilepsy received a median maintenance dose at last follow-up of 400 mg (range 50–650 mg) [50]. In this study, patient retention rates at 1, 2 and 3 years were estimated to be 62, 45 and 35 %, respectively. Improvements in seizure frequency (defined as a reduction in seizure frequency of >50 %) or seizure freedom for at least 6 months were reported in 18 % of patients; ten and four patients were seizure-free for at least 6 and 12 months [50].

Adjunctive therapy with lacosamide was also observed to be effective in three retrospective studies ($n = 500$ [51], 403 [52] and 347 [49]). For instance, in the larger study [51], 44.0, 53.0 and 57.1 % of patients achieved a ≥50 % reduction in seizure frequency after 3, 6 and 12 months, respectively, of adjunctive lacosamide therapy (median daily dosages at the respective timepoints of 200, 300 and 400 mg). At the respective timepoints, 16.0, 15.5 and 14.9 % of patients were seizure-free and retention rates were 96.6, 89.4 and 84.4 % [51].

5 Tolerability

Discussion in this section focuses on tolerability data for lacosamide 200 and 400 mg/day, which are the maintenance dosages approved in the EU (the use of the 600 mg/day dosage is not recommended; see Sect. 4), derived from the three double-blind, multicentre studies discussed in Sect. 4.1 [18–20] and pooled analyses ($n = 1,308$ [including 203 patients who received lacosamide 600 mg/day]) [6, 8, 59, 60] of these studies. Longer-term data from extensions [33–35, 42] of the double-blind, multicentre studies [18–20] and three multicentre studies assessing the tolerability of intravenous lacosamide [36, 61, 62] are also discussed. Limited supplementary data have been procured from ClinicalTrials.gov [55, 63].

The overall adverse event profile with lacosamide was similar between male and female patients and between Caucasian and non-Caucasian patients [8].

5.1 Oral Administration

Oral lacosamide as an adjunct to other AEDs was generally well tolerated in adults and adolescents (aged 16–18 years) with partial-onset seizures, with the majority of adverse events being mild or moderate in intensity [18–20]. In a pooled analysis (available as an abstract) [59], treatment-emergent adverse events (occurring in ≥1 % of patients in any lacosamide treatment group) were reported in 63 % of lacosamide 200 mg/day recipients, 76 % of lacosamide 400 mg/day recipients and 56 % of placebo recipients, with the incidence highest during the titration period. The most frequently reported treatment-emergent adverse events according to another pooled analysis of the three studies are reported in Fig. 1 [8].

Very common (defined as a frequency of ≥1/10 patients) adverse reactions following adjunctive lacosamide in double-blind studies (with an incidence ≥1 % in the lacosamide group and which are >1 % higher than in the placebo group) and from post-marketing experience included diplopia,

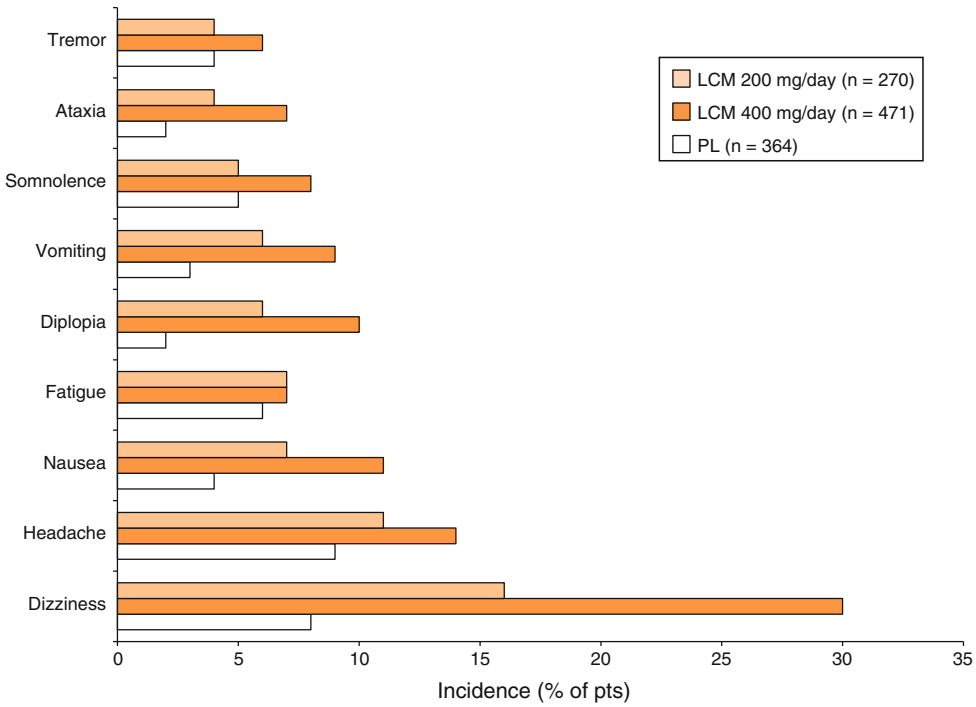

Fig. 1 Tolerability of oral lacosamide, as adjunctive therapy to other antiepileptic drugs, in adults and adolescents (aged 16–18 years) with partial-onset seizures. Incidence of treatment-emergent adverse events affecting >5 % of lacosamide recipients and that were numerically more frequent than in the placebo group in a pooled analysis [8] of three double-blind, multicentre studies of 16 [20] and 18 [18, 19] weeks' duration; see Sect. 4.1 for further dosage and study design details. *LCM* lacosamide, *PL* placebo, *pts* patients

dizziness, headache and nausea [6]. In the individual studies, serious adverse events were reported in 6–9 % of lacosamide recipients and 3–5 % of placebo recipients, with convulsions, dizziness, epileptic seizure, grand mal convulsion and/or psychotic disorder most frequently reported [18–20]. Where reported, there were no individual serious adverse events that occurred at a frequency of >1 % [18], and there were no deaths [19, 20]. Treatment discontinuation because of adverse events occurred in 10 % of lacosamide 200 mg/day recipients, 17 % of lacosamide 400 mg/day recipients and 5 % of placebo recipients [59], with dizziness, ataxia, vomiting, diplopia, nausea, vertigo and blurred vision the most frequently reported adverse events leading to discontinuation [8].

A retrospective pooled analysis (available as an abstract) found that there was no significant difference between the combined lacosamide 200 and 400 mg/day treatment groups and the placebo group in the incidence of treatment-emergent adverse events related to cognition (6.1 vs. 4.7 %; odds ratio [OR] 1.3 [95 % CI 0.7–2.3]) [60]. However, the incidence of treatment-emergent adverse events potentially related to cognition (lacosamide 200 mg/day 1.9 %, OR 0.4 [95 % CI 0.1–1.3]; lacosamide 400 mg/day 8.5 %, OR 1.7 [95 % CI 1.0–3.2]) may be dose related [60]. In Study SP667 [18], there were no clinically important differences observed between the lacosamide and placebo groups with respect to psychiatric adverse events.

Lacosamide appears to have a minimal effect on bodyweight. In the individual studies, the mean changes from baseline to the end of the maintenance period ranged from −0.2 to 0.2 kg for patients receiving lacosamide 200 or 400 mg/day [18–20] and 0.0 kg [20] and 0.6 kg [18, 19] for patients receiving placebo.

Where reported, the incidence of rash was relatively low (4.4 % in lacosamide 400 mg/day recipients vs. 3.8 % in placebo recipients), with all rashes considered mild to moderate in intensity and none considered serious [19].

In clinical studies in adults with partial-onset seizures, alanine aminotransferase levels ≥3 × the upper limit of normal (ULN) were observed in 0.7 % (7 of 935 patients) of lacosamide recipients and 0 % (0 of 356) of placebo recipients [6, 8]. One patient experienced hepatitis (transaminase levels >20 × ULN) and nephritis (proteinuria and urine casts) 10 days following the cessation of lacosamide (dosage not reported) therapy. Transaminases levels returned to normal within 1 month without specific treatment, with the hepatitis/nephritis case interpreted as a delayed hypersensitivity reaction to lacosamide [8].

Longer-term therapy with lacosamide as an adjunct to other AEDs was generally well tolerated in adults and adolescents (aged 16–18 years) with partial-onset seizures [33–35, 42, 55, 63]. In a subgroup analysis (currently available as an abstract) of pooled data from patients in the extension studies who had been exposed only to lacosamide ≤400 mg/day ($n = 363$) [42], 81.3 % of patients experienced at least one treatment-emergent adverse event, with dizziness (occurring in 21.5 % of patients), headache (14.0 %) and nasopharyngitis (10.7 %) the most frequently reported. In the individual extension studies, at least one

serious adverse event was observed in 23.1 % (87 of 376 patients) [35, 55] and 33.8 % (125 of 370) [33, 63] of patients, with convulsion (4.0 % [35, 55] and 6.2 % [33, 63] of patients) the most frequent. In the smallest extension study [34], treatment-emergent serious adverse events were reported in 23.1 % (71 of 308 patients) of patients; 24 of these patients were considered to have treatment-related serious adverse events [34]. Two patients in this extension study died, although none of the deaths were considered to be related to the study medication [34]. Treatment discontinuations because of treatment-emergent adverse events occurred in 8.8–12.7 % of patients [33–35, 55, 63].

5.1.1 Cardiovascular Effects

Adjunctive therapy with lacosamide has been associated with a dose-related prolongation of the PR interval (Sect. 2.1) [6]. Across the three double-blind, multicentre studies [18–20], increases in the mean PR interval at the end of the maintenance period of 4.2–4.6 msec were observed following adjunctive therapy with lacosamide 400 mg/day; where reported [19], the corresponding value in the placebo group was 1.2 ms. There were no reports of cardiac adverse events associated with the prolongation of the PR interval in Study SP754 [19]; in Study SP755 [20], the prolongation of the PR interval did not affect the tolerability profile, and only one lacosamide recipient had an ECG PR interval prolongation reported as an adverse event.

In clinical studies in patients with epilepsy, first degree atrioventricular (AV) block was reported in <1.0 % of lacosamide 200–400 mg/day recipients and 0 % of placebo recipients; no second or higher degree block was observed [6]. However, cases of second and third degree AV block have been observed in post-marketing experience (lacosamide dosage not reported). In clinical studies, syncope was reported in ≤0.3 % of patients receiving adjunctive lacosamide or placebo. In short-term clinical studies there were no reports of atrial fibrillation or flutter; however, both were observed in nonblind studies in patients with epilepsy and in post-marketing experience (incidence and lacosamide dosage not reported) [6]. In Study SP667, two patients (receiving lacosamide 100 mg/day and lacosamide 200 mg/day) developed first degree AV block; both patients continued therapy [18]. Adjunctive lacosamide did not appear to affect heart rate [19], the QRS duration [19, 20] and/or the QT/QTc [18–20] interval.

Longer-term (up to 5 years) therapy with lacosamide as an adjunct to other AEDs was not associated with a change in heart rate or a prolongation of the QTc interval in Study SP756 [34]. However, the mean changes from baseline (of the double-blind core study) in the PR interval at weeks 24, 48 and 168 were 6.3, 8.4 and 10.6 ms, respectively; the mean changes from baseline (of the double-blind study) in the QRS duration at the respective timepoints were 1.4, 0.6 and 0.9 ms, respectively [34].

5.2 Intravenous Administration

The tolerability profile of intravenous lacosamide appears consistent with that of oral lacosamide [8, 36]. When used as a short-term (2–5 days) replacement for oral lacosamide, intravenous lacosamide was generally well tolerated when administered as a 10-, 15- or 30-minute infusion, according to a nonblind, multicentre study [61]. These data are supported by a nonblind multicentre study in 100 patients (aged 16–60 years) with partial seizures in which loading doses (infused over 15 min) of intravenous lacosamide 200, 300 and 400 mg followed by oral lacosamide 100, 150 and 200 mg twice daily, respectively, were, for the most part, well tolerated [62]. However, intravenous administration is associated with local adverse events, such as injection site discomfort or pain, irritation and erythema [8]. In a double-blind, double-dummy, multicentre study, 60 adults with partial-onset seizures who were currently receiving adjunctive oral lacosamide therapy (as part of an extension study) were randomized to receive oral lacosamide plus placebo or intravenous lacosamide (infused over 30 or 60 min) plus placebo twice daily for 2 days [36]. The intravenous lacosamide dosage (200–600 mg/day) administered was the same as the oral lacosamide dosage previously received by the patients in the extension study. No serious adverse events were reported and no patient discontinued therapy because of adverse events.

6 Pharmacoeconomic Considerations

Pharmacoeconomic analyses examined the cost effectiveness of lacosamide as an adjunct to standard therapy with other AEDs versus standard therapy alone in several European [1, 64–69] and North American [70, 71] countries. Most analyses appeared to be based on the same modelling framework (a decision-tree model with 6-month cycles, which followed a hypothetical cohort of 1,000 patients for 2 years [see Table 2 for further details]), which is described in detail in the fully published Belgian analysis by Simoens et al. [64]. The one exception was a UK National Institute for Health and Clinical Excellence (NICE) analysis, which utilized a Markov model and followed a hypothetical cohort of patients with refractory partial seizures for 15 years [1, 69]. Analyses were conducted from the healthcare payer [1, 64–71] and/or societal [70] perspectives. The majority of the analyses are currently available as abstracts [65–68, 70, 71].

In the 2-year analyses, data concerning health states probabilities (based on three states [seizure freedom,

Table 2 Summary of cost-utility analyses of adjunctive lacosamide in the treatment of patients with partial-onset seizures conducted from a healthcare payer perspective [64–68, 70, 71]

Study	Country (year of values)	Lacosamide + standard therapy with other AEDs[a] vs. standard therapy[a] (per pt)			
		Incremental total costs (total costs)	Incremental QALY gained (total QALYs gained)	Incremental cost per QALY gained	% of simulations within WTP threshold[b] (WTP threshold)
European countries					
Benhaddi et al. [65]	Scotland (2008[c])		0.038	£20,017	80 (£30,000)
Benhaddi et al. [66]	Slovak Republic (2011)		0.038	€18,402	83 (€26,500)
Benhaddi et al. [65]	Spain (2008[c])		0.038	€22,771	74.2 (£30,000)
Berggren et al. [67]	Sweden (NR)	€1,000	0.038	€26,700	
Benhaddi et al. [68]	Turkey (2012[c])		0.038	TRY36,392	
Simoens et al. [64]	Belgium (2008)	−€3,619 (€76,941 vs. €80,560)	0.038 (1.240 vs. 1.202)	Dominant	100 (€30,000)
North American countries					
Benhaddi et al. [70]	Canada (2011[c])	$Can1,467 ($Can12,611 vs. $Can11,144)	0.04 (1.24 vs. 1.20)	$Can39,156[d]	~90 ($Can50,000)
Benhaddi et al. [71]	USA (2010[c])		0.038	$US39,574	77 ($US50,000)

Analyses appeared to be based on the same modelling framework (a decision-tree model with 6-month cycles following a hypothetical cohort of 1,000 patients over 2 years). Where reported, annual discount rates for costs and benefits were 3 % [64]

AED antiepileptic drug, *QALY* quality-adjusted life-year, *NR* not reported, *pt* patient, *TRY* Turkish Lira, *WTP* willingness-to-pay

[a] Where reported [64–66, 68, 70, 71], standard therapy included carbamazepine, lamotrigine, levetiracetam, phenytoin, topiramate and/or valproate

[b] Results of sensitivity analyses showing the probability of not exceeding the WTP threshold per QALY gained

[c] Not clearly stated

[d] From a societal perspective, the incremental cost per QALY gained was $Can32,334, with a probability sensitivity analysis revealing that the probability of not exceeding the WTP threshold of $Can50,000 was approximately 90 %

seizure reduction and withdrawal because of a lack of response]) were procured from clinical studies (Studies SP754 [19] and SP755 [20]) [64], with costs and utility values derived from country-specific databases and the literature. Where reported, direct costs included the costs of general practitioner, outpatient and/or emergency department visits (and specialist visits [68, 70, 71], and pre-surgery evaluations and surgery [70] in some analyses), and hospitalization costs [64–66, 68, 70, 71]. Annual discount rates (3 % for both costs and benefits) were reported in the Belgian analysis [64], but not in the abstracts [65–68, 70, 71].

Relative to standard therapy alone, lacosamide plus standard therapy was predicted to be dominant (i.e. less costly and more effective) in Belgium [64] and to be cost effective in Canada [70], Scotland [65], the Slovak Republic [66], Spain [65] and the US [71] from healthcare payer [64–66, 70, 71] and societal [70] perspectives, with incremental costs per quality-adjusted life-year (QALY) gained falling within prespecified willingness-to-pay (WTP) thresholds (Table 2). Moreover, adjunctive therapy with lacosamide resulted in a reduction of approximately 6.7 seizures per patient, relative to standard therapy [64–68, 71], resulting in an incremental cost per seizure avoided of £113 (Scotland) [65], €103 (the Slovak Republic) [66], €107 (Spain) [65], 205 Turkish Lira (Turkey) [68] and $US223 (USA) [71] from a healthcare payer perspective, with the incremental cost per seizure avoided being dominant in the Belgian analysis [64]. Probabilistic sensitivity analyses in Belgium, Canada, Scotland, the Slovak Republic, Spain and the US countries revealed that the probability of not exceeding the prespecified WTP threshold per QALY gained was 74.2–100.0 % (Table 2) [64–66, 70, 71]. In the Turkish analysis [68], the sensitivity analysis revealed that the results were robust.

In the UK NICE analysis [1, 69], data concerning health states probabilities (based on four states [seizure freedom, a 50–99 % reduction in seizure frequency, no response (defined as a <50 % reduction in seizure frequency) and withdrawal because of adverse events]) were procured from clinical studies [18–20]), with costs and utility values derived from UK-specific databases and the literature. Costs (based on 2009–2010 values) and benefits were both discounted at an annual rate of 3.5 % [1, 69].

Adjunctive therapy with lacosamide plus standard therapy versus standard therapy alone was associated with mean costs of £11,777 and £8,928, respectively, a mean gain of 8.24 and 8.197 QALYs, respectively, and an

incremental cost per QALY gained of £66,256, which exceeds the NICE WTP threshold of £20,000 [1, 69].

It should be noted that the cost-effectiveness analyses of adjunctive lacosamide, in common with all pharmacoeconomic analyses, are subject to a number of limitations. Pharmacoeconomic analyses based on clinical studies extrapolate the results of such studies to the general population; however, participant populations, rates of compliance and major outcomes in clinical studies may differ from those observed in real-life practice. In addition, modelled analyses rely on a number of assumptions and utilize data from a variety of sources. Results of pharmacoeconomic analyses may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs.

7 Dosage and Administration

Lacosamide is available in the EU [6], the US [8] and several other countries worldwide. The prescribing information for lacosamide differs across the countries in which it has been approved; therefore, this section focuses on the EU SPC [6]. Local prescribing information should be consulted for detailed information, including contraindications, drug interactions, precautions, and use in special patient populations.

Lacosamide is indicated as adjunctive therapy in the treatment of adults and adolescents (aged 16–18 years) with partial-onset seizures, with or without secondary generalization [6]. It can be administered orally (as a syrup or tablet) or, in patients in whom oral administration is temporarily not feasible, infused over 15–60 min, with direct conversion to or from the oral and intravenous formulations achievable without titration. Lacosamide should be administered twice daily; the recommended initial dosage is 50 mg twice daily (100 mg/day), with the dosage increased to 100 mg twice daily (200 mg/day) after 1 week. In situations where the rapid attainment of lacosamide steady-state plasma concentrations and therapeutic effect are warranted, lacosamide may be initiated with a single loading dose of 200 mg followed approximately 12 h later by a 100 mg twice daily (200 mg/day) maintenance regimen, although there is a potential for a higher incidence of central nervous system adverse events. Depending upon efficacy and tolerability, the maintenance dosage can be increased by 50 mg twice daily (100 mg/day) every week up to a maximum recommended daily dosage of 200 mg twice daily (400 mg/day) [6]. Lacosamide can be administered with or without food [6].

Patients should be monitored for signs of suicidal ideation and behaviours [6]. As with other AEDs, the withdrawal of lacosamide should be gradual (by tapering the daily dose by 200 mg per week) [6].

Adjunctive therapy with lacosamide has been associated with a prolongation of the PR interval (Sect. 5.1.1) [6]. Thus, the use of adjunctive lacosamide is contraindicated in patients with known second- or third-degree AV block, and caution is advised in patients with known conduction problems or severe cardiac disease (e.g. a history of myocardial infarction or heart failure) and particularly in the elderly or those patients receiving concomitant therapy with agents known to be associated with PR prolongation (see Sect. 3.2). Patients should be made aware of the symptoms of second-degree or higher AV block and of atrial fibrillation or flutter [6].

Therapy with lacosamide has been associated with dizziness; therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the agent [6].

The efficacy and tolerability of lacosamide in children and adolescents aged less than 16 years have not yet been established [6]. Currently, there are no adequate data concerning lacosamide in pregnant women; the potential risk of reproductive toxicity is unknown. Therefore, the use of lacosamide during pregnancy is not recommended unless clearly necessary. The EU SPC also recommend that breast-feeding be discontinued during treatment [6]. Recommendations for the use of lacosamide in other special patient populations and in terms of drug interactions are summarized in Sects. 3.1 and 3.2.

8 Place of Lacosamide as Adjunctive Therapy in the Management of Partial-Onset Seizures

The goal of antiepileptic therapy is to achieve seizure freedom with minimal adverse events [1, 72]. However, despite the optimization of all potential therapeutic options, not all patients will achieve complete seizure control. In such patients, the goal shifts to maximizing the reduction of seizure frequency and severity in the absence of toxicity [1, 72].

AEDs are the mainstay of treatment for patients with epilepsy [1]. They are generally recommended by the UK NICE 2012 guidelines for the diagnosis and management of epilepsy [73] after a second epileptic seizure, with the treatment strategy individualized according to a number of factors, including epilepsy syndrome (defined as a distinctive disorder identifiable on the basis of, among others factors, a typical age of onset, seizure type and specific EEG characteristics), seizure type, concomitant therapies and comorbidities, and lifestyle. Of note, AED therapy should be considered after a first unprovoked seizure if, among other factors, the patient has a structural

abnormality (observed on brain imaging) or a neurological deficit, or their EEG demonstrates unequivocal epileptic activity [1]. Therapy should be initiated with a single agent wherever possible, with adjunctive therapy considered when the attempts at AED monotherapy have not resulted in seizure freedom [73]. In patients with refractory partial seizures, the NICE 2012 guidelines [73] recommend adjunctive therapy with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate. Other AEDs that may be considered in those patients in whom initial adjunctive therapy is ineffective or not tolerated include eslicarbazepine acetate, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide and lacosamide [73].

The pharmacokinetics of an AED play an important role in selectability [72]. The ideal AED should, among other criteria, have a linear absorption (thus permitting its bioavailability to be predicted), minimal or no protein binding (specifically albumin binding) and linear kinetics metabolism [72]. The majority of oral AEDs currently in use are passively absorbed (with the exception of gabapentin, pregabalin and potentially phenytoin) and exhibit a broadly ranging degree of protein binding, with over 50 % of carbamazepine, lamotrigine, phenytoin, tiagabine and valproic acid protein bound [72]. Lacosamide differs to commonly used AEDs in that it undergoes rapid absorption and has high oral availability and low protein binding (Sect. 3). In general, lacosamide appears to have low interaction potential, with the pharmacokinetics of other commonly used AEDs (including carbamazepine, levetiracetam, lamotrigine, phenobarbital, phenytoin, valproic acid and zonisamide) unaffected by coadministration with lacosamide (Sect. 3.2). However, limited data suggest a potential pharmacodynamic interaction between lacosamide and other voltage-gated sodium channel-blocking AEDs (e.g. carbamazepine, lamotrigine, phenytoin) [Sect. 2]. Further investigation is required to confirm or exclude such an interaction. Lacosamide is not expected to affect the pharmacokinetics of digoxin, metformin, omeprazole or oral ethinylestradiol/levonorgestrel, or the exposure of midazolam. There was no evidence of interactions between lacosamide and warfarin (Sect. 3.2).

The ideal AED should also be available in multiple formulations [72], thereby permitting flexible administration across different scenarios. For instance, parenteral AED administration may be required in emergency situations, with AED solutions able to be administered via nasogastric, gastric or rectal tubes to patients unable to reliably swallow (e.g. infants, patients with gastrointestinal disturbances) [72]. Lacosamide is available orally (as a syrup or tablet) and as an intravenous infusion, with direct conversion to or from the oral and intravenous formulations achievable without dose adjustment (see Sects. 3 and 7).

The exact mechanism of action of lacosamide is as yet unclear; however, unlike carbamazepine, lamotrigine and phenytoin, it has no apparent effect on the fast inactivation of voltage-gated sodium channels, instead selectively enhancing the slow inactivation of voltage-gated sodium channels, thereby stabilizing hyperexcitable neuronal membranes and inhibiting repetitive neuronal firing (Sect. 2). In vitro, neither lacosamide nor O-desmethyl lacosamide appear to bind with high affinity to a broad range of animal or recombinant human receptor sites or ion channels (Sect. 2). In general, oral lacosamide as an adjunct to other AEDs was associated with seizure control in adults and adolescents (aged 16–18 years) with partial-onset seizures (Sect. 4). In three randomized, double-blind, placebo-controlled, multicentre studies (Sect. 4.1), significantly greater median percentage changes from baseline to the end of the maintenance period in seizure frequency per 28 days were observed with lacosamide 400 mg/day versus placebo (ITT and per-protocol populations). In the two studies that assessed the lacosamide 200 mg/day dosage, a significant between-group difference over placebo in this endpoint was observed in the ITT population of one, but not the other, study and in the per-protocol populations of both studies. The proportions of patients achieving a $\geq$50 % change from baseline in seizure frequency were significantly higher with lacosamide 400 mg/day in the ITT and per-protocol populations of all three studies and with lacosamide 200 mg/day in the per-protocol population of one study.

Importantly, the antiepileptic efficacy of adjunctive lacosamide is not limited to patients meeting rigorous selection criteria in placebo-controlled, multicentre studies. Evidence from noncomparative extension studies suggest that lacosamide is also effective with longer-term treatment, with the antiepileptic efficacy of adjunctive lacosamide therapy sustained for up to 8 years (Sect. 4.2). Findings from observational and retrospective studies in the clinical setting provide further support for the efficacy and retention of lacosamide (Sect. 4.4). Furthermore, pooled analyses of the three placebo-controlled, multicentre studies demonstrated that lacosamide was effective irrespective of the concomitant AEDs used or whether the concomitant AED regimen included at least one sodium channel-blocking agent (Sect. 4.3). Head-to-head studies comparing adjunctive lacosamide with other AEDs would be of interest.

Lacosamide also demonstrated beneficial effects on health-related outcomes that were sustained over the longer-term, with significant improvements in the Seizure Severity total score and in the seizure worry and social functioning subscale scores following 48 weeks'

adjunctive lacosamide therapy. Over one-third of patients demonstrated clinically meaningful improvements in all QOLIE-31 subscale scores at week 48, with the mean improvements in both the QOLIE-31 and the SSQ remaining stable for up to 5 years of therapy (Sect. 4.3). Further health-related quality of life data for lacosamide would be of interest.

Although beyond the scope of this review, it is worth noting that the use of lacosamide as a monotherapy in adults and adolescents (aged 16–18 years) with partial-onset or generalized tonic-clonic seizures and as an adjunctive therapy in children with partial-onset seizures is a current focus of interest in ongoing clinical studies, with one study [74] and its extension [75] assessing the efficacy and tolerability of converting to lacosamide monotherapy.

Oral lacosamide as adjunctive therapy in combination with other AEDs was generally well tolerated in adults and adolescents (aged 16–18 years) with partial-onset seizures (Sect. 5.1). Dizziness was the most frequently reported treatment-emergent adverse event, with the EU SPC advising patients to exercise caution until they are familiar with the potential effects of the agent (see Sect. 7). The tolerability profile of intravenous lacosamide appears consistent with that of oral lacosamide (Sect. 5.2), although intravenous administration is associated with local adverse events, such as injection site discomfort or pain, irritation and erythema [8]. Of note, lacosamide appears to have a minimal effect on bodyweight (Sect. 5.1).

Adjunctive therapy with lacosamide has been associated with a dose-related prolongation of the PR interval [6]. However, in the three studies discussed in Sect. 5.1.1, PR interval prolongation was only reported as an adverse event in one lacosamide recipient. First degree AV block has been reported in <1.0 % of lacosamide 200–600 mg/day recipients in clinical studies; however, no second or higher degree block was observed. Cases of atrial fibrillation or flutter, and second and third degree AV block, have been reported in post-marketing experience with adjunctive lacosamide (dosage not reported) and more data are required to assess the cardiovascular effects of the drug. Of note, adjunctive lacosamide is contraindicated in patients with known second-or third-degree AV block and caution is advised in other patient subgroups (see Sect. 7).

The potential for psychotropic effects with AED therapy is related to both direct (mechanism of action, polytherapy, toxicity and withdrawal) and indirect (epilepsy- or patient-related) mechanisms [76, 77], with a previous personal or familial psychiatric history associated with an increased risk of developing psychiatric adverse events, predominately depression [76]. Although there have been reports in double-blind studies and from post-marketing experience of confusional state, depression and insomnia (frequency of ≥1/100 to <1/10) and aggression, agitation, euphoric mood, hallucination, psychotic disorder, suicidal ideation and suicide attempt (frequency of ≥1/1,000 to <1/100) with adjunctive lacosamide therapy [6], a recent review [78] has not identified adjunctive lacosamide therapy as being more frequently associated with psychiatric adverse events. Currently available data do not exclude the possibility of an increased risk of suicidal ideation and behaviour with lacosamide and, thus, the EU SPC currently recommends that patients be monitored for psychiatric adverse events (see Sect. 7) [6].

For all AEDs, the prevalence of malformations in the offspring of women treated for epilepsy is two- to three-fold higher than the rate (~3 %) observed in the general population [6]. Moreover, an increase in offspring malformations has been noted with polytherapy [6]. In a retrospective analysis (currently available as an abstract) of pooled data from all clinical studies assessing the efficacy of oral or intravenous lacosamide, 10 pregnancies were confirmed in women receiving lacosamide 200–800 mg/day [79]. As women with confirmed pregnancy tests were withdrawn from the studies, the overall lacosamide exposure was limited to the first trimester. Five pregnancies were completed, and no infants had evidence of major congenital abnormalities. However, the overall risk of lacosamide prenatal exposure remains unknown [79] and the EU SPC does not recommend the use of lacosamide during pregnancy unless clearly necessary (see Sect. 7) [6].

Taking into account the trends in prescribing patterns towards newer and more expensive AEDs, the costs of treating patients with epilepsy are likely to increase [1]. Mixed results regarding the cost effectiveness of adjunctive lacosamide were observed in pharmacoeconomic modelling studies (Sect. 6). Relative to standard therapy alone, lacosamide plus standard therapy was predicted to dominate (i.e. less costly and more effective) in Belgium and to be cost effective in Canada, Scotland, the Slovak Republic, Spain and the US, with incremental costs per QALY gained falling within prespecified WTP thresholds. However, in the UK NICE analysis, the incremental cost per QALY gained with adjunctive therapy with lacosamide plus standard therapy relative to standard therapy alone exceeded the NICE WTP threshold (Sect. 6). Of note, when discussing the individual cost of epilepsy, other aspects, including lost employment, hospital visits and overall life disruption/quality of life, also need to be carefully considered [1]; thus, further well-designed pharmacoeconomic analyses are needed to help clarify the relative cost-effectiveness of lacosamide to other AEDs in the treatment of partial-onset seizures.

In conclusion, oral lacosamide (administered for an initial titration period followed by a 12-week maintenance period) as an adjunctive therapy to other AEDs generally provided better seizure control than placebo in adults and

adolescents (aged 16–18 years) with partial-onset seizures participating in well designed studies, with efficacy sustained during longer-term (up to 8 years) treatment. Oral and intravenous lacosamide were generally well tolerated in this patient population, with the majority of adverse events being mild or moderate in severity. Thus, oral and intravenous lacosamide as an adjunctive therapy to other AEDs provides a useful option in the treatment of patients with partial-onset seizures.

Data selection sources: Relevant medical literature (including published and unpublished data) on lacosamide was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 21 October 2013], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Lacosamide, epilepsy, seizure, seizures.
Study selection: Studies in patients with partial-onset seizures who received lacosamide as adjunctive therapy. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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