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A long-term noninterventional safety study of adjunctive lacosamide therapy in patients with epilepsy and uncontrolled partial-onset seizures

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ABSTRACT

This noninterventional, observational, postauthorization safety study (SP0942, NCT00771927) evaluated the incidence of predefined cardiovascular- (CV) and psychiatric-related treatment-emergent adverse events (TEAEs), in patients with epilepsy and uncontrolled partial-onset seizures, when initiating adjunctive therapy with lacosamide or another approved antiepileptic drug (AED) according to standard medical practice. Active recording of predefined TEAEs of interest took place at three-monthly recommended visits for up to 12 months. Of 1004 patients who received at least one dose of adjunctive AEDs, 511 initially added lacosamide therapy, 493 added another AED, 69 were ≥65 years of age, and 72 took concomitant antiarrhythmic drugs. Patients in the lacosamide cohort had a higher median frequency of partial-onset seizures (6.0 versus 3.5 per 28 days) despite taking more concomitant AEDs (84.9% versus 66.9% took ≥2) at baseline. Patients who added lacosamide took a modal dose of 200 mg/day over the treatment period (n = 501), and 50.1% (256/511) completed 12 months of treatment. Fifty-one point nine percent (256/493) of patients who added another AED completed the study, with the most commonly added AED being levetiracetam (28.4%). Four patients (0.8%) in each cohort, all <65 years of age, reported predefined CV-related TEAEs. None were considered serious or led to discontinuation. One event each of sinus bradycardia (lacosamide), atrioventricular block first degree (lacosamide), and syncope (other AED) were judged to be treatment-related. Another patient in the other AED cohort reported bradycardia while taking concomitant antiarrhythmic drugs. Predefined psychiatric-related TEAEs were reported by 21 patients (4.1%) in the lacosamide cohort and 27 patients (5.5%) in the other AED cohort. Depression was the most common to be treatment-related (7/11 and 12/18 of patients reporting treatment-related psychiatric TEAEs, respectively). Serious psychiatric-related TEAEs were reported by four patients who added lacosamide (two cases of depression, two of suicide attempt) and one who added another AED (depression). Seven deaths occurred, all of which were considered unrelated/unlikely related to study medication. This thorough evaluation revealed a low incidence of predefined CV- and psychiatric-related TEAEs in patients taking adjunctive AED therapy according to standard medical practice. No specific safety concerns related to adjunctive lacosamide therapy were noted.

1. Introduction

Lacosamide is a functionalized amino acid with proven efficacy as an antiepileptic drug (AED). In Europe, lacosamide is currently approved as an adjunctive therapy for the treatment of partial-onset seizures (POS) in adult and adolescent (16–18 years of age) patients with epilepsy, at dosages up to 400 mg/day (200 mg twice a day) [1]. Lacosamide is approved in several other countries, including the United States, where it is licensed for use as a monotherapy or adjunctive therapy in patients (≥17 years of age) with POS [2].

Pharmacokinetic studies have shown lacosamide to have minimal protein binding, high oral absorption, dose-proportional bioavailability,

Abbreviations: AE, adverse event; AED, antiepileptic drug; AV, atrioventricular; CV, cardiovascular; ECG, electrocardiogram; PASS, postauthorization safety study; POS, partial-onset seizures; PTSD, posttraumatic stress disorder; SAE, serious adverse event; SS, safety set; TEAE, treatment-emergent adverse event.

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a half-life that allows twice-daily dosing, and low risks of drug–drug interactions [3,4]. Three Phase II/III, double-blind, randomized registration trials confirmed the safety and efficacy of lacosamide in more than 1300 patients with POS, each randomized to receive 200, 400, or 600 mg/day lacosamide or placebo, to be taken adjunctive to one to three baseline AEDs [5–7]. The treatment-emergent adverse events (TEAEs) most frequently reported during the registration trials were central nervous system- and gastrointestinal-associated. The most common drug-related adverse events (AEs), namely dizziness and nausea, also showed a relationship with dose [5–7]. Similar types of TEAEs were observed in short-term studies of adjunctive lacosamide therapy via intravenous administration, in long-term open-label studies for up to 8 years, and when taken as monotherapy [8–13].

Cardiac conduction side effects are associated with the use of several AEDs, particularly those that block sodium channels [14–17]. A small dose-related increase in the PR interval has been observed in trials of oral and intravenous lacosamide, with no significant change in blood pressure or QTc interval [11–13,18–20]. There have also been some published reports of cardiac AEs in patients receiving lacosamide [9,18,21–28].

Some AEDs have a known potential for recreational abuse [29–31]. While a few euphoria cases were reported during pharmacokinetic and human abuse studies, overall, euphoria was rarely (<1% of patients) reported during the lacosamide development program [2,32].

Psychiatric conditions exist at a higher prevalence among patients with epilepsy than in the general population, including depression, anxiety, and aggression disorders [33,34]. Some AEDs have shown potential associations with psychiatric AEs and behavioral changes [35–37]. Psychiatric-related AEs (such as depression) are commonly listed in AED labeling, including that for lacosamide [1,2].

AEDs in general may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. A class warning is in place and acknowledged in all AED product labeling [35,38–40]; however, the mechanism for this increased risk is unknown. The overall efficacy and safety of adjunctive lacosamide use for the treatment of uncontrolled POS was established in well-controlled clinical studies.

Postauthorization, noninterventional studies provide data which are complementary to that obtained from randomized, placebo-controlled studies, which are generally conducted in more optimized treatment settings. Postauthorization, observational studies include patients with diverse characteristics and comorbidities, reflective of the patient population who receive that medication in real-life, according to the product label and summary of product characteristics. Flexible drug selection and dosing reflects the standard medical care received by patients in the real-world, where medical supervision may also be less intensive than in controlled studies, and treatment decisions may be influenced by additional factors. Patients in these studies may also have more control over their own treatment, including care decisions and medication compliance. In this way, the lack of controlled factors during postauthorization, noninterventional studies is of great benefit, as the results provide a 'snap-shot' on the effectiveness of medications in the way that they are currently used in real-life. This observational, postauthorization safety study (PASS) of lacosamide provides complementary data to that obtained during the three registration trials, and was conducted as a commitment to the European Medicines Agency to specifically assess the incidence of predefined cardiovascular (CV)- and psychiatric-related TEAEs in patients with uncontrolled POS who use lacosamide in routine clinical practice.

2. Methods

2.1. Study design

This noninterventional PASS (SP0942, NCT00771927) was conducted at 71 sites in France, Germany, the Netherlands, Spain, and the United Kingdom. Patients were assigned to one of two cohorts based on the decision to prescribe lacosamide or another AED, made by the treating physician prior to enrollment and according to standard medical practice. Eligible patients were enrolled within 2 days of treatment initiation in blocks of 10 per physician: five who added lacosamide and five who added another AED. These patients formed the "lacosamide cohort" and the "other AED cohort", respectively. Treatment continued per standard local medical practice for up to 12 months, allowing flexible treatment according to individual patient need and physician's judgment. It was recommended that follow-up visits occurred at 3, 6, 9, and 12 months, with an additional safety visit 2 weeks after the end of treatment if adjunctive treatment was discontinued before the end of the study. A routine electrocardiogram (ECG) was conducted at each study visit if part of the site's standard medical practice.

2.2. Patients

Patients aged 16 years or older with a diagnosis of epilepsy and experiencing POS considered by the treating physician to be uncontrolled on current therapy were assigned adjunctive AED therapy. The study protocol was approved by an independent ethics committee. All patients provided written consent and were treated in accordance with local regulations and the Declaration of Helsinki.

2.3. Study variables

The primary safety variables for this study were the incidence of predefined CV- and psychiatric-related TEAEs (Table 1). Treatment-emergent adverse events were defined as AEs occurring during treatment or within 30 days of the last dose. All AEs were reported to or observed by the physician at every visit, with additional active collection of predefined CV- and psychiatric-related TEAEs using a checklist. The recording physician also assessed the intensity and relationship of each AE to the study treatment. Relationships of "possible", "probable", or "highly probable", or entries with missing relationship data, were classified as drug-related. The intensity of each TEAE was categorized based on the impact caused to routine activities in daily life. Adverse events with missing intensity entries were categorized as severe. Other safety variables included the overall incidence of TEAEs and serious AEs (SAEs), and TEAEs leading to discontinuation of the added AED.

The modal daily dose of lacosamide taken during the treatment period was calculated for each patient. This was used to calculate the overall mode of the modal daily doses in the lacosamide cohort.

Although not predefined, several other variables were evaluated, if captured as part of routine clinical practice: the occurrence of TEAEs, changes in vital signs and body weight, the median percent change in seizure frequency per 28 days from the 2-month retrospective baseline, the Clinical Global Impression of Change questionnaire for the

Table 1
Predefined cardiovascular- and psychiatric-related treatment-emergent adverse events.

Cardiovascular[a]		
Adams–Stokes syndrome	AV block second degree	Sinus bradycardia
AV block	Syncope	ECG PR prolongation (201–209 ms)
AV block complete	Bradycardia	
AV block first degree	Bradyarrhythmia	
Psychiatric[a]		
Depression	Intentional self-injury	Substance abuse
Major depression	Self-injurious behavior	Substance abuser
Depressed mood	Self-injurious ideation	Polysubstance dependence
Depression suicidal	Poisoning deliberate	Intentional drug misuse
Completed suicide	Drug abuse	Intentional overdose
Suicidal behavior	Drug abuser	Multiple drug overdose, intentional
Suicidal ideation	Drug dependence	
Suicide attempt		

AV, atrioventricular; ECG, electrocardiogram.
[a] Medical Dictionary for Regulatory Activities (MedDRA, Version 15.0) preferred terms.