A Report on Comparative Safety and Efficacy of Lacosamide in the treatment of Partial Onset Seizures

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Introduction

A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. "Epileptic seizure" is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. "Epilepsy" is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction[1]. A seizure provoked by a reversible insult (e.g., fever, hypoglycemia) does not fall under the definition of epilepsy because it is a short-lived secondary condition, not a chronic state[2].

"Epilepsy syndrome" refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, EEG findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs). The nonspecific term "seizure disorder" should be avoided[2].

Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per year per 100,000 population[3]. About 1% of the population suffers from epilepsy, and about one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more appropriately chosen antiepileptic medications or other therapies). Approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures[2].

Seizures are divided into three categories: generalized, focal (formerly called partial), and epileptic spasms. Focal seizures originate in neuronal networks limited to part of one cerebral hemisphere. Generalized seizures begin in bilateral distributed neuronal networks. A seizure can begin focally and later generalize. Seizures can originate in the cortex or in subcortical structures. Using a detailed history, EEG findings, and ancillary information, a physician can often categorize the seizure/epilepsy type, after which an appropriate diagnostic evaluation and treatment plan is formulated[4-6].

The main subtypes of generalized seizures are absence, generalized tonic–clonic (GTC), myoclonic, and atonic. Absence seizures (formerly called petit mal) involve staring with unresponsiveness to external verbal stimuli, sometimes with eye blinking or head nodding. GTC seizures (formerly called grand mal) consist of bilateral symmetric convulsive movements (stiffening followed by jerking) of all limbs with impairment of consciousness. Myoclonic seizures consist of sudden, brief ("lightning-fast") movements that are not associated with any obvious disturbance of consciousness. These brief involuntary muscle contractions may affect one or several muscles; therefore, myoclonic seizures can be generalized or focal. Atonic seizures involve the loss of body tone, often resulting in a head drop or fall. Epileptic spasms can occur at any age; when they begin in the first year of life, they comprise a syndrome called infantile spasms (IS)[4-6]. Lennox–Gastaut syndrome (LGS) is a childhood epileptic encephalopathy, of heterogeneous etiologies, which is characterized by multiple seizure types (most commonly tonic, atypical absence, and drop attacks)[7].

Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide only since 2000. It was initially approved in the US only as adjunctive therapy for partial-onset seizures. However, more recent trials earned it approval as adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures of juvenile myoclonic epilepsy, and a recent comparative monotherapy trial earned it approval for use as initial monotherapy in Europe[8].

Eslicarbazepine acetate, developed by Sunovion Pharmaceuticals, approved by USFDA in 2013, is a new anti-epileptic drug belonging to the dibenzazepine carboxamide family that is currently approved as adjunctive therapy and monotherapy for partial-onset (focal) seizures. The drug enhances slow inactivation of voltage-gated sodium channels and subsequently reduces the activity of rapidly firing neurons[9].

Oxcarbazepine, developed by Novartis Pharmaceuticals, approved by USFDA in 2000, is an anticonvulsant and voltage-sensitive sodium channel antagonist approved as an adjunctive therapy or monotherapy for Partial Seizures[10-13].

Lacosamide (LCM) was approved in 2008 in the European Union and in the USA as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults and adolescents with

epilepsy[14]. LCM selectively enhances slow inactivation of sodium channels; it also binds to the collapsin response mediator protein-2 (CRMP-2) and modulates mCRMP2 function[15-17].

Pharmacokinetic data[18-21]

Innovator	UCB Pharmaceuticals
Regulatory Approval	USFDA – 2008, CDSCO - 2010
Patent Information	DP: 27/03/2022 (INH-IPM)
Pregnancy Category	C, DEA Schedule - V
Dose & Dosage form	Tablet - 50mg, 100mg, 150mg, 200mg; Syrup – 15mg/ml, IV – 200mg/20ml
ROA	Oral, Injection
Approved Indications	Indicated as an adjunctive therapy in the treatment of partial-onset seizures in patients with Epilepsy aged 17 years and older
Indications under trial	Preregistration: Tonic-Clonic Epilepsy
Bioavailability	Approximately 100%
Time to peak	0.5 to 12 hours
Protein binding	< 15%
Metabolism	CYP2C19
Elimination T½	13 hours
Excretion	Renal
Contraindications	None

Comparison of Safety[18, 22-24]

Parameter	Lacosamide	Oxcarbazepine	Eslicarbazepine acetate	Levetiracetam
				Indicated for adjunctive

Approved Indications	Indicated as an adjunctive therapy in the treatment of partial-onset seizures in patients with Epilepsy aged 17 years and older	Indicated as a monotherapy or adjunctive therapy for partial-onset seizures	Indicated as an adjunctive therapy for partial-onset seizures in adults	therapy in the treatment of: Partial onset seizures in patients one month of age and older with epilepsy, Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy.
Adverse Effects	Headache – 13%, Dizziness - 31%, Somnolence – 7%, Diplopia – 11%, Blurred Vision – 8%, Ataxia – 8%, Tremor – 7%, Nystagmus – 5%, Diarrhea - 5%, Abdominal pain – 10%, Pruritus – 2%, Nausea – 11%, Vomiting – 9%, Fatigue – 9%, Depression – 2%	Headache – 32%, Dizziness -26%, Somnolence – 20%, Diplopia – 14%, Ataxia – 9%, Tremor – 3%, Nystagmus – 7%, Insomnia – 4%, Hyponatremia – 3%, Constipation – 2%, Diarrhea, Dyspepsia – 5%, Abdominal pain – 10%, Rash – 3%, Nausea – 15%, Vomiting – 13%, Fatigue	Headache – 15%, Dizziness -28%, Somnolence – 18%, Diplopia – 11%, Blurred vision – 5%, Ataxia – 6%, Tremor – 4%, Depression – 3%, Insomnia, Hypertension, Hyponatremia, UTI, Memory impairment, Constipation, Diarrhea, Abdominal pain – 2%, Rash – 3%, Nausea –	Headache – 15%, Somnolence – 9%, Dizziness, Aggression, Fatigue, Cough, Lethargy – 5%, Abdominal pain – 8%, Diarrhea, Decreased appetite, Nasal congestion – 2%

		– 15%	16%, Vomiting – 10%, Fatigue – 7%	
Warnings & Precautions	Dosage adjustment is recommended in patients with mild – moderate hepatic or severe renal impairment. Suicidal Behavior and Ideation. Caution is advised for patients with known cardiac conduction problems [e.g., second-degree atrioventricular (AV) block], who are taking drugs known to induce PR interval prolongation, or with severe cardiac disease such as myocardial ischemia or heart failure. Patients should be advised that it may cause syncope.	No dose adjustment is recommended in patients with mild to moderate liver impairment and mild-moderate renal impairment. Suicidal Behavior and Ideation, Serious Dermatologic Reactions, Hyponatremia: Monitor sodium levels in patients at risk or patients experiencing hyponatremia symptoms. Multi-organ hypersensitivity, Seizure risk aggravation.	No dose adjustment is recommended in patients with mild to moderate liver impairment and mild renal impairment. Suicidal Behavior and Ideation, Serious Dermatologic Reactions, Hyponatremia: Monitor sodium levels in patients at risk or patients experiencing hyponatremia symptoms. Drug Induced Liver Injury Withdrawal of Eslicarbazepine: Withdraw gradually to minimize the risk of increased seizure frequency and status	Dosage adjustment is required in patients with renal impairment. No dose adjustment is recommended in patients with liver impairment. Suicidal Behavior and Ideation, Behavioral abnormalities including psychotic symptoms, suicidal ideation, irritability, and aggressive behavior have been observed, Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on Levetiracetam, Withdrawal Seizures: Levetiracetam must be

	Abrupt withdrawal may increase the seizure frequency.		epilepticus.	gradually withdrawn

Comparison of Efficacy[18, 22-24]

Outcome	Lacosamide	Oxcarbazepine	Eslicarbazepine acetate	Levetiracetam
Median percent reduction in Partial Seizure frequency	40%	40.2%-49.9%	36%-39%	26.1%-30.1%

Conclusions

- Lacosamide, developed by UCB Pharmaceuticals, approved by USFDA in 2008, is an anticonvulsant and an enhancer of voltage-sensitive sodium channel inactivation, approved as an adjunctive therapy for Partial Seizures.
- The efficacy of Lacosamide is greater than that of Levetiracetam in the treatment of Partial Seizures. The efficacy is almost similar to that of the lower limit of Oxcarbazepine and the upper limit of Eslicarbazepine.

- Safety wise, it has been labeled under DEA schedule V. Less number of adverse effects has been reported with Levetiracetam, while almost similar adverse effects were reported with the use of other drugs. In patients with hepatic or renal impairment; Oxcarbazepine seems to be a better choice.
- Indications wise, Levetiracetam covers most of the types of Epilepsies, while the other three drugs are exclusive for Partial Seizures.
- To conclude, it can be said that, the safety vs. efficacy profile of Lacosamide is good.

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