A Report on Comparative Safety and Efficacy of Cenobamate 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].

Cenobamate, developed by SK Life Science Inc, approved by USFDA in 2020, is an anticonvulsant that works by inhibiting voltage gated sodium currents, approved as a monotherapy or adjunctive therapy for Partial Seizures in adults[18].

Pharmacokinetic data[18-21]

Innovator	SK Life Science Inc.
Regulatory Approval	USFDA - 2020
DEA Class	Schedule – V (Controlled – Substance)
Patent Information (INH-IPM)	DS Patent expiry – 30/10/2027(Ext. if granted 30/10/2032), NCE expiry – 10/03/2025
Pregnancy Category	May Cause Fetal harm (based on animal data)
Dose & Dosage form	Tablet – 25mg, 50mg, 100mg, 150mg, 200mg
ROA	Oral
Approved Indications	Indicated as a monotherapy or adjunctive therapy for partial-onset seizures in adults
Indications under trial	Phase – III: GTCS
Bioavailability	Not Specified
Time to peak	1 – 4 hours
Protein binding	60%
Metabolism	UGT2B7, UGT2B4, CYP2E1, CYP2A6, CYP2B6
Elimination T½	50 – 60 hours
Excretion	Urine, Feces
Contraindications	Contraindicated in patients with familial short QT syndrome and in patients with hypersensitivity to the drug.

Comparison of Safety[18, 23-25]

Parameter	Cenobamate	Lacosamide	Oxcarbazepine	Eslicarbazepine acetate	Levetiracetam
Approved Indications	Indicated as a monotherapy or adjunctive therapy for partial-onset seizures in adults	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 in patients aged 2 years and older	Indicated as an adjunctive therapy for partial-onset seizures in adults	Indicated for adjunctive 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 – 12%, Dizziness – 22%, Somnolence – 22%, Dyspnea – 3%, Diplopia – 7%, Blurred Vision – 2%, Ataxia – 3%, Tremor – 3%, Nystagmus – 7%, UTI – 5%, Nasopharyngitis – 4%, Constipation – 4%, Diarrhea – 3%, Nausea – 6%, Vomiting – 4%, Liver enzyme elevation – 1%	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 – 15%	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 – 16%, Vomiting – 10%, Fatigue – 7%	Headache – 15%, Somnolence – 9%, Dizziness, Aggression, Fatigue, Cough, Lethargy – 5%, Abdominal pain – 8%, Diarrhea, Decreased appetite, Nasal congestion – 2%
Warnings & Precautions	Caution must be exerted and dosage adjustment is recommended in patients with mild-moderate	Dosage adjustment is recommended in patients with mild – moderate hepatic or severe renal	No dose adjustment is	No dose adjustment is recommended in patients with mild	Dosage adjustment is required in patients with renal impairment. No

Warnings & Precautions	renal or hepatic impairment. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity, QT Shortening, Suicidal Behavior and Ideation, Neurological Adverse Reactions, Abrupt withdrawal may increase the seizure frequency.	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. Abrupt withdrawal may increase the	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.	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 epilepticus.	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 gradually withdrawn

		seizure frequency.			

Comparison of Efficacy[18, 23-25]

Outcome	Cenobamate	Lacosamide	Oxcarbazepine	Eslicarbazepine acetate	Levetiracetam
Median percent reduction in Partial Seizure frequency	55.6%	40%	40.2%-49.9%	36%-39%	26.1%-30.1%

Conclusions

- Cenobamate, developed by SK Life Science Inc, approved by USFDA in 2020, is an anticonvulsant that works by inhibiting voltage gated sodium currents, approved as a monotherapy or adjunctive therapy for Partial Seizures in adults.
- The efficacy of Cenobamate in treating Partial Seizures is superior to that of all the comparators in this study, next to it are Oxcarbazepine and Lacosamide.

- Safety wise, DEA has labeled Cenobamate and Lacosamide as controlled substances and placed them under Schedule-V. Levetiracetam has the least number of reported adverse effects, 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 Cenobamate like the other comparators is indicated for Partial Seizures and additionally it is in Phase III clinical trials for Generalized Tonic Clonic Seizures.
- To conclude, it can be said that the overall safety vs. efficacy profile of Cenobamate is balanced owing to its great efficacy.

References

1. Shorvon SD, Andermann F, Guerrini R. (ed.). 2011. The causes of epilepsy. Cambridge University Press, Cambridge.
2. Carl E. Stafstrom and Lionel Carmant. Seizures and Epilepsy: An Overview for Neuroscientists. Cold Spring HarbPerspect Med. 2015 Jun; 5(6): a022426.
3. Hauser W, Hersdorffer D. 1990. Epilepsy: Frequency, causes and consequences. Demos, New York.
4. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, Glauser TA, Mathern GW, Moshe SL, et al. 2010. Revised terminology and concepts for organization of seizures and epilepsy: Report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51: 676–685.
5. Berg AT, Millichap JJ. 2013. The 2010 revised classification of seizures and epilepsy. Continuum (MinneapMinn) 19: 571–597.
6. Muro VM, Connolly MB. 2014. Classifying epileptic seizures and the epilepsies. In Epilepsy (ed. Miller JW, Goodkin HP), pp. 10–14. Wiley, Chichester, UK.
7. Camfield P. (2011) Definition and natural history of Lennox–Gastaut syndrome. Epilepsia 52(Suppl. 5): 3–9.
8. BasselAbou-Khalil. Levetiracetam in the treatment of epilepsy. Neuropsychiatr Dis Treat. 2008 Jun; 4(3): 507–523.

9. Graciana L. Galiana et al. Eslicarbazepine Acetate: A New Improvement on a Classic Drug Family for the Treatment of Partial-Onset Seizures. Drugs R D. 2017 Sep; 17(3): 329–339.
10. Bosak M,Słowik A,Iwańska A,Lipińska M,Turaj W, Co-medication and potential drug interactions among patients with epilepsy. Seizure. 2019 Jan 16.
11. Di Stefano G,Maarbjerg S,Truini A, Trigeminal neuralgia secondary to multiple sclerosis: from the clinical picture to the treatment options. The journal of headache and pain. 2019 Feb 19.
12. Jansen AC,Andermann E, Progressive Myoclonus Epilepsy, Lafora Type 1993.
13. Caraballo RH,Cachia P,Valenzuela GR,Calvo A, Rasmussen syndrome: absence seizures may be induced by oxcarbazepine. Epileptic disorders: international epilepsy journal with videotape. 2019 Feb 15.
14. Bauer S, Willems LM, Paule E, Petschow C, Zöllner JP, Rosenow F, Strzelczyk A. The efficacy of lacosamide as monotherapy and adjunctive therapy in focal epilepsy and its use in status epilepticus: clinical trial evidence and experience. Ther Adv Neurol Disord. 2017 Feb;10(2):103-126. doi: 10.1177/1756285616675777. Epub 2016 Nov 29. PMID: 28382109; PMCID: PMC5367645.
15. Heers C, Lees G, Errington A, Stoehr T. Lacosamide selectively enhances sodium channel slow inactivation. Epilepsia. 2007;48:320.
16. Errington A, Stöhr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. Mol Pharmacol. 2008;73:157–169.
17. Freitag JM, Beyreuther B, Heers C, Stoehr T. Lacosamide modulates collapsin response mediator protein 2 (CRMP-2) Epilepsia. 2007;48:320.
18. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. XCOPRI *(cenobamate).* PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212839s000lbl.pdf.
19. DEA. DIVERSION CONTROL DIVISION. Available Online: https://www.deadiversion.usdoj.gov/fed_regs/rules/2020/fr0310_9.htm#:~:text=Based%20on%20these%20data%2C%20DEA,21%20U.S.C.

20. USFDA. ORANGE BOOK. Available online: https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=006&Appl_No=212839&Appl_type=N.
21. ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/results?cond=&term=cenobamate&cntry=&state=&city=&dist=.
22. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. VIMPAT (lacosamide). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022253lbl.pdf.
23. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. BRAND TRILEPTAL (oxcarbazepine). PRESCRIBING INFORMATION. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021014s036lbl.pdf.
24. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. APTION (eslicarbazepine acetate). PRESCRIBING INFORMATION. Available online:https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022416s000lbl.pdf
25. HIGHLIGHTS OF PRESCRIBING INFORMATION. FDA. KEPPRA (levetiracetam). PRESCRIBING INFORMATION. Available online:https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021035s078s080,021505s021s024lbl.pdf.