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Conceptual and molecular docking study of newly developed antiepileptic drug cenobamate

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Abstract

In the past two decades, there has been sudden development in antiepileptic drugs (AEDs) for the adjunctive treatment of epilepsy. CNB is a leading-edge new generation tetrazole-derived carbamate for the treatment of focal-onset epileptic seizures where the mode of action is mediated by blocking voltage-gated sodium channels and interaction with the GABAergic system. The US FDA approved CNB with new hope for superior control over seizure, better safety, and tolerability profile compared to earlier AEDs.

Keywords: Cenobamate; Tetrazole derivative; Focal-onset seizure; Computational study; Anticonvulsant

Highlights

- Cenobamate (CNB) is a novel tetrazole alkyl carbamate derivative being developed by SK life science Inc.
- CNB received its first approval on 21 November 2019 in the United States for the treatment of partial-onset seizures.
- It has been approved by the European Commission on 31st March 2021

1. Introduction

Epilepsy is one of the world's oldest chronic neurological disorders characterized by recurrent predictable seizures that affect over 1% of the world population of all ages. The currently marketed drugs (AEDs) provide seizure control in only 70% of the patients at the cost of undesirable side effects and toxicity which are dose-related. Research for novel agents with enhanced potency having fewer side effects is necessary today to treat epileptic seizures [1,2].

The latest antiepileptic drug, CNB has been approved by the US FDA on Nov 21, 2019, under the brand name Xcopri®. CNB used in the treatment of focal onset seizure is a novel tetrazole-alkyl carbamate derivative with one chiral center. CNB with a high level of efficacy is anticipated to act by blocking GABAergic voltage-gated sodium channels and interaction with the GABAergic system. The high potency of the drug is associated with the possibility of significant rash and lesser tolerability at higher doses. Suggesting that there is an additional need for investigating the safety profile and actual clinical value [3–5]. The 2D and 3D structure of CNB is represented in **Fig (1).**

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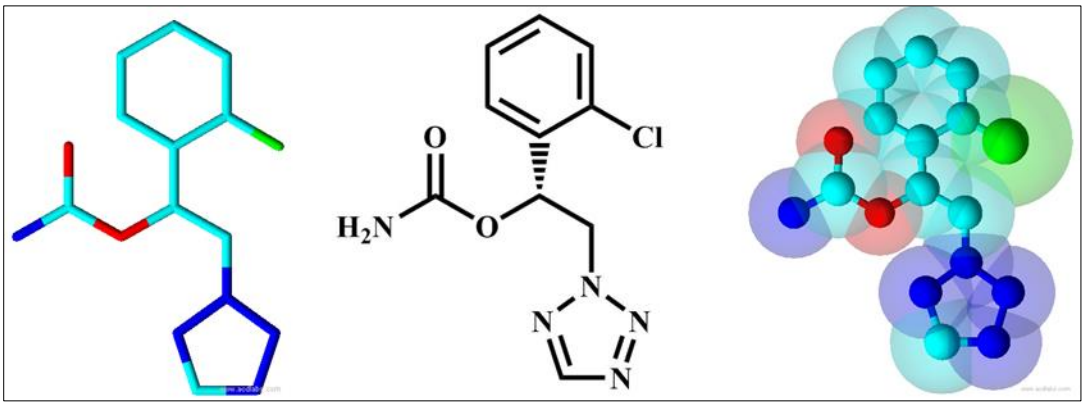

Figure 1 2D and 3D Structure

2. Chemistry

CNB is an alkyl-monocarbamate derivative, chemically it is s [(1R)-1-(2-chlorophenyl)-2-(tetrazol-2-yl) ethyl] carbamate. The molecular formula of CNB is $C_{10}H_{10}ClN_5O_2$ and the molar mass is 267.67 g/mol [6]. It is a white to off-white crystalline powder that has good solubility in water (1.7 mg/mL) and is even more solubilized in organic solvents like ethanol (209.4 mg/mL) [FDA, 2019]. The synthetic route of Cenobamate is shown in **Fig (2)** as described in the literature [7].

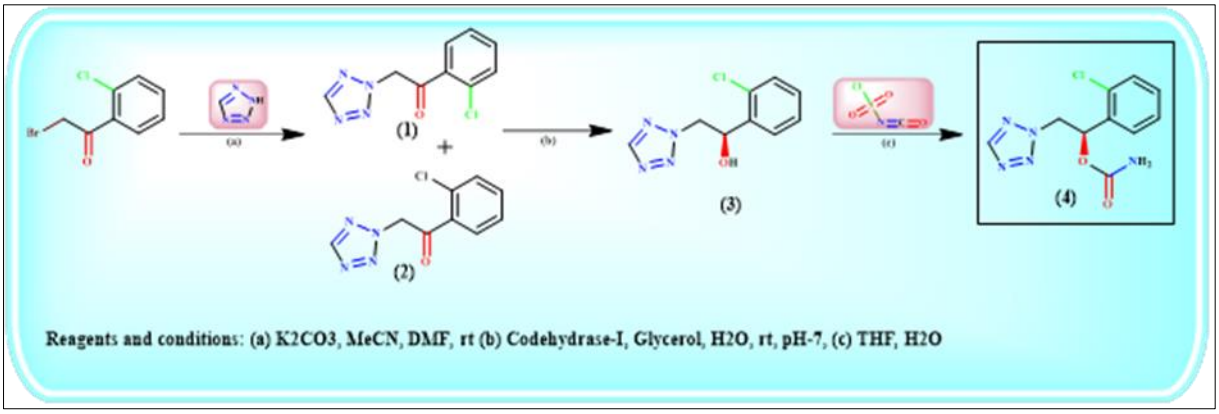

Figure 2 Synthetic route of CNB

3. Pharmacophore model

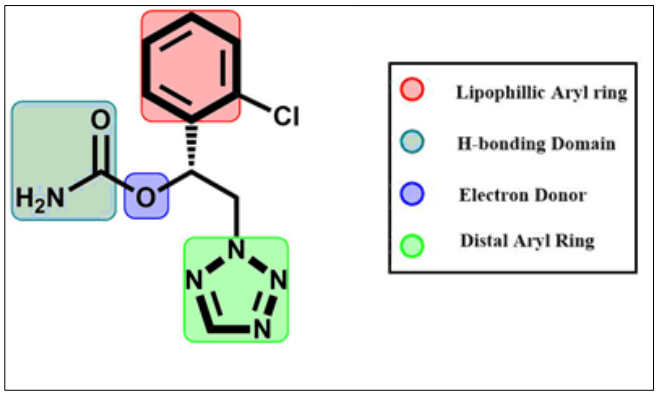

Figure 3 Dimmock's Model of CNB

The interactions at the binding site have been proposed by Dimmock et al. [8,9] in which the pharmacophoric elements were considered to be in the lipophilic aryl ring and hydrogen bonding domain. Also, a detailed aryl ring attachment. An attachment of the second aryl ring to the proximal aryl ring increases the van der Waal's bonding at the binding site and increases the potency [10,11]. The Dimmock model for the anticonvulsant activity of Cenobamate is shown in **Fig (3).**

4. Pharmacology

4.1. Mechanism of Action

The exact mechanism of CNB is unknown. However, CNB has been demonstrated to inhibit the fast and slow inactivation of sodium channels at therapeutic doses and diminish repetitive neuronal firing by blocking voltage-gated sodium currents in patients with partial-onset seizures [12-14]. At 2-3 times the maximal therapeutic dose it also modulates the $GABA_A$ ion channel in a positive allosteric manner [12-15] **Fig (4).**

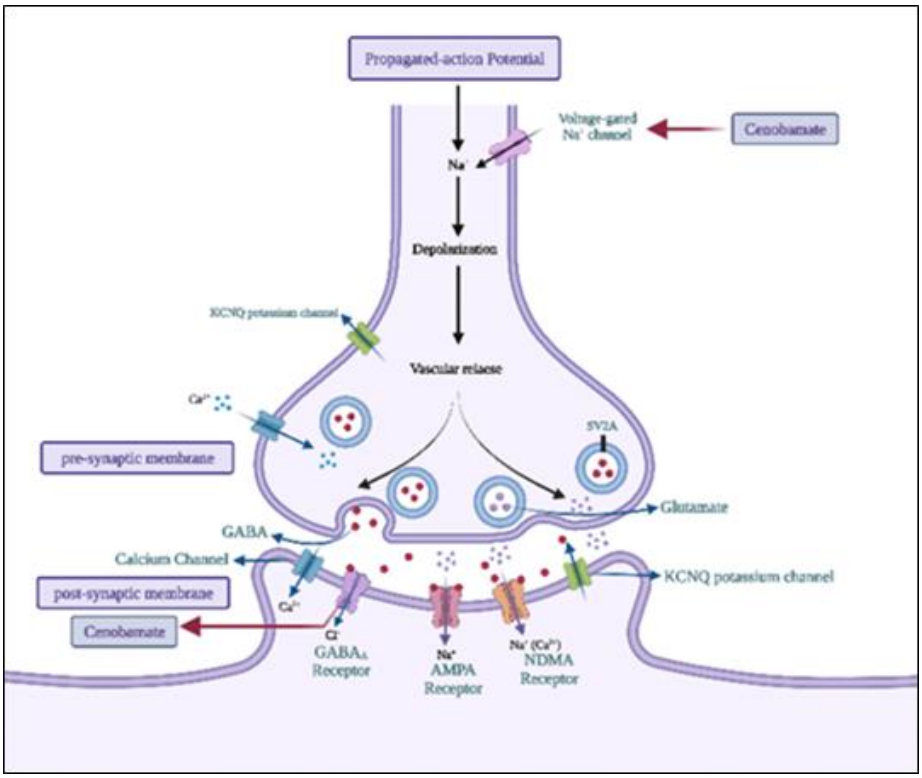

Figure 4 Mechanism of Action [18]

4.2. Pharmacokinetics

AUC for CNB increases faster than dose-proportional manner following a single oral dose from 5 to 750 mg. The Cmax of CNB rises in a dose-dependent manner. A steady-state plasma concentration is reached after about two weeks of daily administration. Cmax for CNB increases dose proportionately after a single oral dose (range 5–750 mg) or multiple doses (range 50–300 mg/day), but increases in AUC for CNB are greater than dose-proportional after a single oral dose of 5 to 750 mg. Approximately 88 % of a CNB dose is absorbed after oral administration, and the time to peak plasma concentration in the majority of patients is 1–4 hours. CNB pharmacokinetics is unaffected by food. Once-daily oral administration of CNB for two weeks results in steady-state plasma concentrations of CNB. It is bound 60% to plasma proteins, mostly human albumin. It is estimated that after oral administration, its apparent volume of distribution is between 40 and 50ml. It has a terminal half-life of 50-60 hours and an oral clearance of 0.45-0.63 L/hour at doses greater than 100 mg to 400 mg/day. The drug is predominantly metabolized through Glucuronidation mainly by UGT2B7 and also via UGT2B4; oxidation primarily via CYP2E1, CYP2A6, CYP2B6, and to a lesser amount by CYP2C19 and CYP3A4/5. A mean of 93.0 % of the total radioactive dosage was recovered in urine (87.8%) and faeces (5.2%) after administration of radiolabeled CNB. Within 72 hours of dosage, almost half of the radioactivity had been eliminated [16-17]. The data is represented in Table (1).

Table 1 Pharmacokinetics of CNB

property	Cenobamate
Bioavailability	88%
Cmax	Increase dose proportionally
Tmax	1-4 hour
Food effect	Unaffected
Volume of distribution (Vd)	40-50 mL
Protein binding	60% (Albumin)
Major drug-metabolizing enzyme	Glucuronidation (UGT2B7, UGT2B4) Oxidation (CYP2E1, CYP2A6, CYP2B6)
Apparent half-life	50-60 hour
apparent oral clearance	0.45-0.63 L/hour
Route of elimination	5.2% in Feces and 87.8% in Urine

4.3. Computational parameters

The physicochemical properties of Cenobamate were calculated from ChemDraw professional 16.0 and Marvin Sketch 21.20 software and the data is presented in **Table (2).**

Table 2 Physio-chemical properties

Properties	values
Physical state	Solid
Colour	White powder
Melting point	96.8-98.3°C
Boiling point	520.8±60.0 °C at 760 mmHg
Density	1.6±0.1 g/cm3
Solubility	Aqueous solubility (1.7 mg/mL) Solubility in organic solvents (209.4 mg/mL)
Vapour pressure	0.0±1.4 mmHg at 25°C
Enthalpy of vaporization	79.4±3.0 kJ/mol
Flash point	268.8±32.9 °C
Inder of refraction	1.688
Polarizability	24.42
Logp	1.98
pKa	14.28 (Strongest Acidic) -1.7 (Strongest basic)
Henry's law	6.31

4.4. In silico ADME

ADME properties of the compound were predicted using a QikProp study, Schrodinger Maestro 11, running on a Linux x64 operating system and the Data is represented in Table (3).

Table 3 In-silico ADME properties

Title	[a]MW	[b]Donor HB	[c]AccptHB	[d]LogPo/w	% Human[e] Oral Absorption	[f]Rule Of Five
Range	< 500	≤ 5	≤ 10	< 5	>80% high <25% poor	≤ 1
Cenobamate	267.674	2	6	0.987	73.496	0

[a]Molecular weight of the molecule; [b]Estimated number of hydrogen bonds that would be donated by the compound to water molecules in an aqueous solution; [c]Estimated number of hydrogen bonds that would be accepted by the compound from water molecules in an aqueous solution; [d]Predicted octanol/water partition coefficient; [e]Oral absorption for oral bioavailability of compounds; [f]violations of Lipinski's rule of five

4.5. Molecular Docking

Molecular docking study of Cenobamate was done for predicting the possible binding modes and to identify the interacting residues. The analysis was done for the two targets; $GABA_A$ receptor and human neuronal voltage-gated sodium channel. The interaction of the compound with receptor or enzyme using Glide extra precision (XP) Maestro 10.1 Schrodinger, running on Linux x64 operating system, was done with the help of X-ray crystal structure data. The 3D crystal structure of $GABA_A$ (PDB ID: 4COF) and voltage-gated sodium channel (PDB ID: 2KAV) was acquired from RCSB Protein Data Bank (http://www.pdb.org). Docking studies were carried out for the selection and composition of protein, grid binding, and proper alignment of the molecule at the active site of the receptor based on the docking score of the ligands along with the hydrogen bonds & π- π interaction formed with the amino acid residues of the protein Table (4). Prime Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) method was used to calculate the binding energies and ligand strain energies in Maestro 10.1. Ligands and receptors were separately prepared by using Lig Prep and Protein preparation wizard. The structure of the ligand was finally taken from the pose viewer file (Glide output). The binding analysis poses of the compound were examined by the free energy score.

The docking analysis showed that the drug participates in hydrogen bonding and pi-pi interaction. The docking score (in kcal/mol) found while interacting with the $GABA_A$ receptor was -5.392 and Glide energy was -34.191 kcal/mol. The Drug showed five H-bonds (Gln185, Lys274, Glu52, and Val50). A nitrogen of the tetrazole ring produces H-bond with Gln185 and Lys274. The carbonyl group attached to urea made a hydrogen bond interaction with Lys274 and Amide group forms H-bond with Glu52 and Val 50 as shown in **Fig (5).** Interaction of Cenobamate with voltage-gated sodium channel showed a docking score of -3.421 kcal/mol and glide energy -29.096 kcal/mol. While interacting with the sodium channel the drug forms 2 hydrogen bonding with Ser 1869 and Glu1785 one with nitrogen of tetrazole ring and amide group of urea substitution respectively as shown in **Fig (6).**

Table 4 Docking interactions of CNB with $GABA_A$ and sodium channel receptors

Ligand	Receptor	Binding Energy/Docking score (kcal/mol)	Interaction Residues	Hydrogen Bonding	Hydrogen Bond Length (Å)
Cenobamate	GABAAT	-5.392	Pro 184, Gln 185, Phe 186, Pro 273, Ser 51, Met 49, Asp 48, Asn 54, Val 53, Lys274, Glu52, and Val50	Gln185, Lys274, Glu52, and Val50	2.31, 2.20, 2.37, 1.66, and 1.81
	Voltage-gated sodium channel	-3.421	Gly 1870, Ser 1869, Glu 1868, Leu 1866, Val 1865, Leu 1790, Pro 1789, Glu 1788, Glu 1785	Ser 1869, and Glu1785	2.30 and 1.91

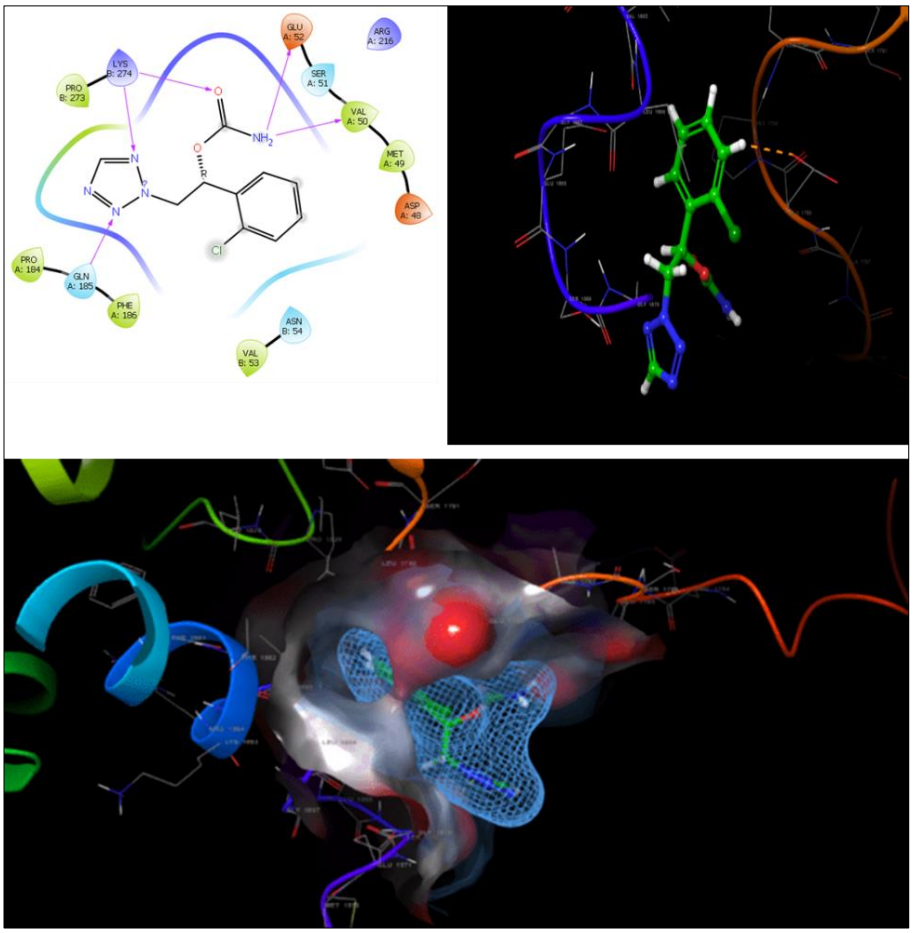

Figure 5 Upper left panel: 2D LigPlot of Cenobamate in the binding site of Gamma-aminobutyric acid showing hydrogen bond and pi-cation interactions. Upper right panel: 3D Docked pose of Cenobamate in the binding site $GABA_A$ showing hydrogen bond interactions with Gly185, Lys274, Glu52, and Val50 (PDB ID: 4COF). Lower Panel: Receptor surface view of the compound in the binding site of $GABA_A$ receptors

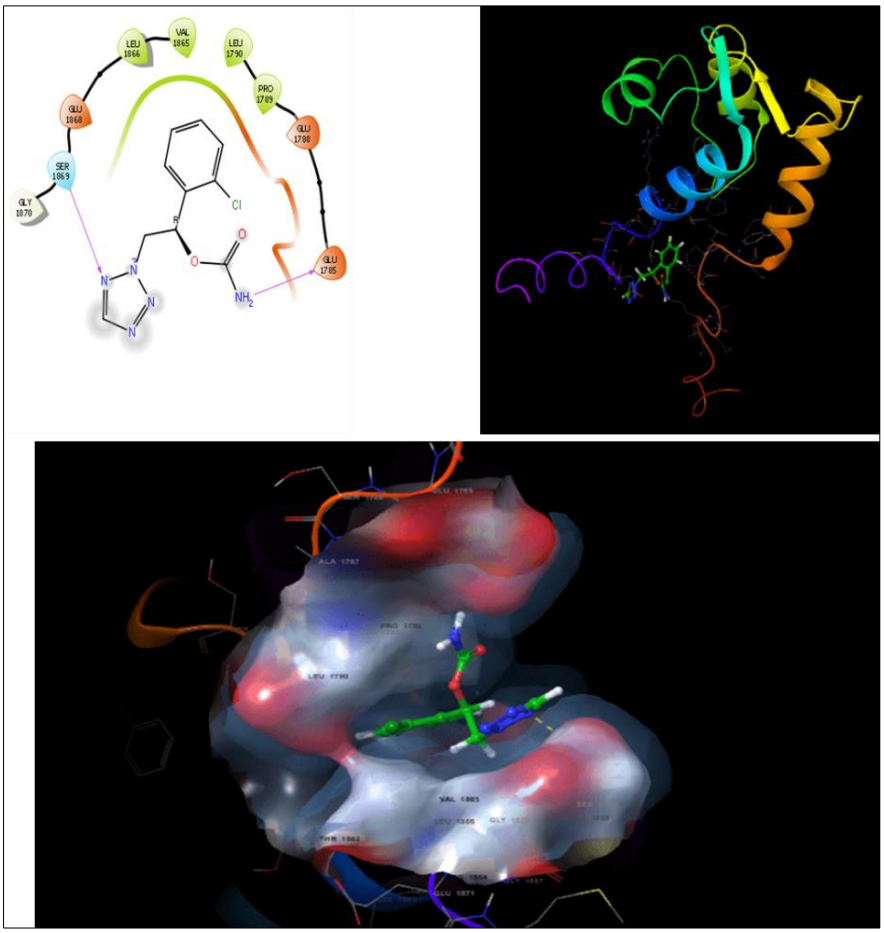

Figure 6 Upper left panel: 2D LigPlot of Cenobamate in the binding site of Human neuronal voltage-gated sodium channel showing hydrogen bond and pi-cation interactions. Upper right panel: 3D Docked pose of Cenobamate in the binding site Cenobamate in the binding site of Human neuronal voltage-gated sodium channel showing hydrogen bond interactions with Ser1869 and Glu1785 (PDB ID: 2KAV). Lower Panel: Receptor surface view of the compound in the binding site of Voltage-gated sodium channel

4.6. Spectral Prediction

The conceptual IR values were compiled for CNB as per the structure. The theoretical ^{1}H NMR, ^{13}C NMR, and mass spectra were predicted by ChemDraw professional 16.0. **Fig (7-9).**

IR (cm^{-1}): 3450 (NH_2), 3010 (CH, Ar), 2860 (CH, Alip), 1690 (C=O), 1650 (CN), 1585 (N=N), 1520 (C=C), 1140 (CO), 743 (C-Cl); ^{1}H NMR (ppm): 4.42 (S, 2H, CH_2), 6.0 (S, 1H, CH); 7.16 (S, 2H, NH); 7.21-7.68 (M, 4H, Ar-H), 9.45 (S, 1H, CH); ^{13}C NMR (δ ppm) 64.7, 68.1, 127.0, 128.5, 129.0, 129.0, 132.0, 137.3, 152.0, 158.2; Mass spectrum [m/z: relative abundance]:267: 1.00 268: 0.13 269: 0.33 270: 0.04 Elemental C, 44.87%, H, 3.77%, Cl, 13.24%, N, 26.16%, O, 11.95%.

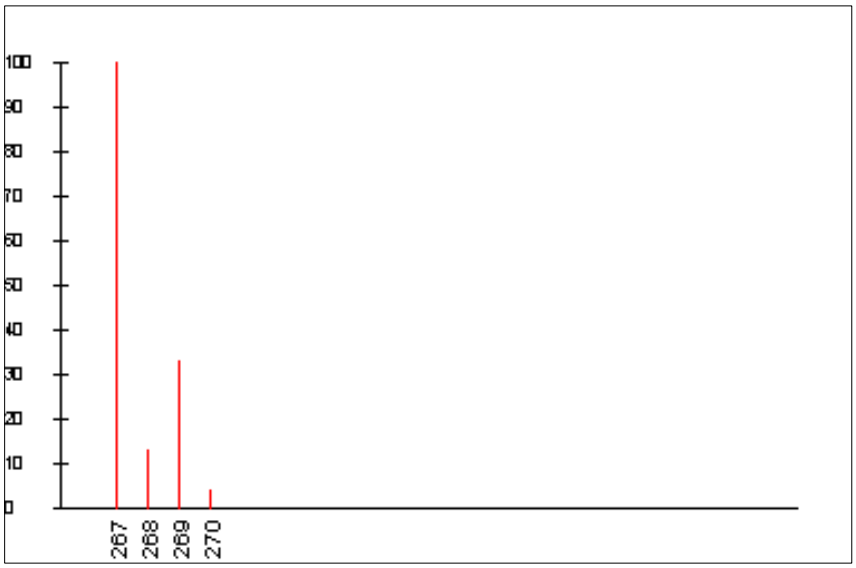

Figure 7 Mass spectrum of CNB

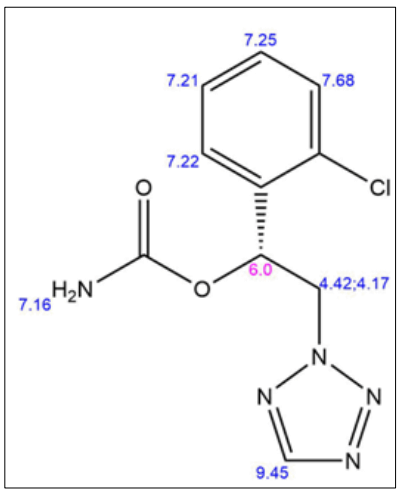

Figure 8 1H NMR

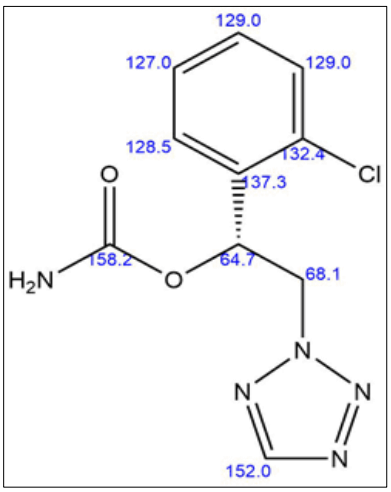

Figure 9 13C NMR

4.7. Contraindications [FDA, 2019]

- CNB or any of the inactive components in CNB can cause hypersensitivity.
- Contraindicated in patients with familial short QT syndrome.

4.8. Drug interactions

CNB lowers the plasma concentration of AEDs like lamotrigine (LTG) and carbamazepine (CBZ), it is best to increase the dose while taking them together [FDA, 2019]. It raises the plasma levels of AEDs such as phenytoin, phenobarbital, and desmethylclobazam, enhancing the risk of dose-related side effects. As a result, the dose of these medications should be modified when taken with CNB. When combined with CNB, it lowers the plasma levels of CYP2B6 and CYP3A substrates and reduces the impact of drugs that work through these substrates. It is advised that the dose be increased. When combined with CNB, it raises the plasma concentration of CYP2C19 Substrates, which may increase the risk of adverse effects. As a result, dose modifications are required. It also reduces the efficacy of oral contraceptives by reducing plasma levels, requiring the use of additional non-hormonal contraceptives [FDA, 2019] [18].

4.9. Indications

The active ingredient of Xcopri is CNB used for the treatment of partial-onset seizures in adults. Available in a table of 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg [FDA, 2019].

4.10. Side effects

Cenobamate is reported to be well tolerated by epileptic patients [19], however, some common and serious side effects or life-threatening allergic reactions may occur with the use of the medicament.

Common side effects: these effects may disappear during treatment as the body gets adjusted to the drug over a time period and does not need medical attention. These include Headache, Nausea, vomiting, skin rashes, fatigue, constipation, and vertigo, loss of appetite, diplopia, dizziness and loss of coordination.

Serious side effects: serious or life-threatening allergic reactions may occur with serious health issues. These may include abnormal heart rhythm, suicidal thoughts, breathlessness, depression, yellow eyes and muscle pain.

Multiorgan susceptibility, commonly known as drug rash with eosinophilia and systemic symptom (DRESS) syndrome, has been noticed. Fever, rash, lymphadenopathy, and/or facial swelling are common symptoms of DRESS, related to multiple organ system involvements such as liver, kidney disorders, haematological irregularities, myocarditis, or myositis, which may result in acute viral infection. This disorder can exhibit itself in a variety of ways and may affect other organ systems [20-21].

4.11. Regulatory status

CNB received the US FDA approval on 21st November 2019 for the treatment of partial-onset seizures in adult patients and on 31st March 2021[FDA, 2019], Arvelle Therapeutics received European Commission (EC) approval for CNB with the brand name ONTOZRY® for the adjunctive treatment of focal onset seizures with or without secondary generalisation in adults who have not been adequately controlled seizures despite a history of treatment with at least two AEDs [22]. On 23rd December 2021 SK biopharmaceutical entered into a licencing agreement with Endo International to commercial CNB in Canada. On 15 December 2021, Arvelle Therapeutics announced that National Institute for Health and Clinical Excellence (NICE) recommended CNB as an option for the treatment of focal onset seizures with or without secondarily generalization of seizures in adult patients with drug-resistant epilepsy that has not been adequately controlled with at least two AEDs [23].

4.12. Current prospective

Phase-III study (NCT04557085, YKP3089C035), evaluating the safety and efficacy of CNB for adjunctive therapy for the treatment of partial-onset seizure is ongoing and initial results are expected by the end of October 2023 [24]. Phase-III study (NCT05067634, YKP3089C040) evaluating the safety and efficacy of CNB in pediatric patients (2-17 years) for the treatment of partial-onset seizure is ongoing and the study is expected to be complete by the end of 2024 [16]. Phase I (NCT04903314, YKP3089C039), an Open-Label, randomized study for Dose-Escalation of CNB in Paediatric patients With Partial-Onset seizures is continuing and the result is expected by the end of December 2022 [21]. Phase-III (NCT03678753, YKP3089C025) randomized, double-blind study evaluating the safety and efficacy of CNB adjunctive treatment for primary generalized tonic-clonic seizures is ongoing and primary results are expected in the mid-2023 [22]

5. Conclusion

CNB a new generation antiseizure drug is for the treatment of partial focal seizure in addition to other antiepileptic drugs. The potent anticonvulsant profile displayed by CNB is likely due to the presence of pharmacophoric elements and LogP value which is enough to allow delivery of the drug to the active site.

The review provides an overview of the latest novel molecule CNB as a new perspective for the treatment of epilepsy.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors have no conflict of interest for publication of this paper.

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