Epilepsy has been traditionally thought of as a family of disorders leading to recurrent seizures rather than a single disease. The International League Against Epilepsy (ILAE) definition of a seizure is abnormal, excessive or synchronous neuronal activity in the brain. These atypical stimuli often lead to sudden or transient alterations of consciousness, loss of voluntary motor control, or changes in autonomic function. If the area of abnormal activity can be localized, it is considered a partial (or focal) seizure. If it encompasses both hemispheres, it is classified as a generalized seizure. Partial and generalized seizures can be further broken down by presentation, for example, a tonic-clonic seizure is characterized by a period of sustained muscle contraction followed by a period of rhythmic spasms involving the same muscle groups. A 2015 CDC report showed over 65 million people worldwide and 3.5 million in the US suffer from epilepsy. This accounts for nearly 1% of the population, making it one of the most common neurological disorders globally. Low socioeconomic status and lack of proper care contribute largely to the burden of illness within this demographic leading many people to go untreated. In addition, those afflicted with the disease suffer from significantly lower Health Related Quality of Life (HRQOL). The national economic burden of epilepsy is estimated at $12.5 billion with a per-patient-per-year cost of $10,000. Over 80% of this is associated with indirect costs related to loss of productivity. Overall, medication prices contribute relatively little to direct costs of this disease state and those controlled on antiepileptic drugs incur much lower annual costs associated with inpatient resources and work absenteeism, than those that are uncontrolled or untreated.

While diagnosis of epilepsy relies on amount and frequency of seizures, it is highly debated what kind of seizures can be classified under the umbrella term of epilepsy. For example, drug-induced or febrile seizures can be cause for concern, but multiple episodes of these would not be considered epilepsy. In short, a seizure is an event, while epilepsy is the uncontrolled, unprovoked occurrences of these events. The ILAE and the International Bureau for Epilepsy (IBE) released an operational definition as having either two or more unprovoked seizures within 24 hours, one unprovoked seizure with a high risk of 10-year recurrence, or a diagnosis of an epileptic syndrome (a syndrome in which epilepsy is a predominate feature i.e. Lennox-Gastaut). There are over 20 Anti-Epileptic Drugs (AEDs) and choice of first line agent is based on seizure type, cost, adverse effects, and pharmacokinetic profile. Some of the most common first line agents for partial-onset seizures are oxcarbazepine, lamotrigine, phenytoin, and valproic acid. While monotherapy with these AEDs is effective in controlling seizure activity in half the population, the rest will require multiple medications and one-third will be refractory, meaning seizures persist despite treatment with two or more drugs. Additionally, these drugs are associated with many adverse events and may not increase the overall quality of life of these patients.

Xcopri® (cenobamate) is a novel azole derivative that received an early approval for treatment of partial-onset seizures in adults based on two promising phase II studies. It is attempting to fill the gaps in therapy associated with treatment refractory seizures while having a superior safety profile. This article aims to review the safety and efficacy of cenobamate in the treatment of patients with uncontrolled partial-onset seizures.

**Mechanism of Action**

Cenobamate has been shown to inhibit both persistent and slow voltage gated sodium currents in a dose dependent manner. It is also an allosteric modulator of GABAA ion channels. The exact mechanism of action in epilepsy is not known, however, the combination of effects on these ion channels has shown to reduce neuronal firing.

**Pharmacokinetics**

Cenobamate bioavailability is approximately 90% after oral administration and median time to peak plasma concentration was between one and four hours. Steady state was reached after two weeks of once daily oral administration. High fat meals did not affect absorption. It is 60% bound to plasma proteins and the terminal half-life is 50-60 hours. Cenobamate is metabolized mainly by glucuronidation through UGT2B7 and UGT2B4. For
oxidative metabolism, CYP2E1, CYP2A6, and CYP2B6 are the main enzymes involved. CYP2C19 and CYP3A4/5 play a lesser role in oxidative metabolism. Radiolabeled cenobamate showed 88% excretion in the urine.

**Pharmacodynamics**

Studies were performed to observe the interactions with cenobamate and ethanol. No significant differences were observed when measuring attention, psychomotor performance, and memory test in healthy subjects. Doses of 400 mg led to reports of euphoria in an early phase abuse potential study. Physical dependence was also observed, and abrupt discontinuation could lead to seizures. Cenobamate shortened QTc intervals in a dose dependent manner. While no studied doses reduced the QTc interval to less than 300 ms, one-third of patients on 200 mg and two-thirds of patients on 500 mg showed QTc shortening of greater than 20 ms.

**Clinical Trials**

Currently, there is only one published trial evaluating the safety and effectiveness of cenobamate. While the outcomes for a second phase II trial have been included in the package insert, the results are only published as an abstract rather than a full peer-reviewed article.

**Phase II Trial**

Krauss et al. conducted a phase II multi-centered, randomized, double-blinded, placebo controlled, dose response trial looking at the safety and efficacy of cenobamate in 437 patients with partial-onset seizures despite treatment with one to three AEDs. Exclusion criteria included patients taking diazepam, phenytoin, or phenobarbital within one month of screening (drug interactions). Additional exclusion criteria included patients that had taken vigabatrin within the past year, felbamate for less than 18 months consecutively, or a benzodiazepine rescue treatment within the past month. Patients with status epilepticus within the past three months or suicidal ideation within the past six months were also excluded. An electroencephalogram (EEG) confirmation of focal epilepsy was required for inclusion. An eight-week period was used to prospectively assess baseline seizure type (focal aware, motor, focal impaired awareness, or focal to bilateral tonic-clonic seizures) and frequency before randomization. Patients required a baseline seizure frequency of four per 28 days and could not have a seizure free period greater than 25 days.

Patients were then randomized 1:1:1:1 to receive either cenobamate 100mg daily (n=108), 200 mg daily (n=100), 400 mg daily (n=111), or placebo (n=106). Patients in each group were initiated on cenobamate 50 mg daily followed by a four week titration increasing the dose by 50 mg per week until a dose of 100 mg or 200 mg was achieved. Those allocated to the 400 mg arm were then further titrated for two weeks at 100 mg per week until the 400 mg daily dose was reached. Patients that could not tolerate dose increases were maintained at the previous dose. All treatment groups followed an intention to treat (ITT) protocol. Following the titration phase, a 12-week maintenance phase included patients on the maximum attained dose of cenobamate. The primary endpoints were the percentage change from baseline in focal seizure frequency averaged over 28 days of the entire 18-week study period and responder rates, defined as a greater than or equal to 50% reduction from baseline during the maintenance phase only. Safety outcomes included the incidence of treatment-emergent adverse events, serious adverse events, discontinuations due to adverse events, and clinical laboratory evaluations assessing changes from baseline in vital signs, 12-lead electrocardiograms (ECGs), physical and neurological examinations, and the Columbia-Suicide Severity Rating Scale responses.

Overall, 360 of the 437 (82%) patients completed the study. For the primary endpoints, the median percentage change from baseline in focal seizure frequency per 28 days during the 18-week study was −24.3% (IQR −45 to −7.0%) for the placebo group, −36.3% (−62.5 to −15.0%; p=0.0071) for the cenobamate 100 mg group, and −55.2% for both cenobamate 200 mg group (−73.0% to −23.0; p<0.0001) and 400 mg group (−85.0% to −28.0; p<0.0001). Responder rates during the 12-week maintenance phase were as follows: 25% (26 of 102 patients) in the placebo group, 40% (41 of 102; OR 1.97, 95% CI 1.08–3.56; p=0.0365) for the cenobamate 100 mg group, 56% (55 of 98; OR 3.31, 95% CI 2.06–5.49; p<0.0001) for the cenobamate 200 mg group, and 64% (61 of 95; OR 5.24, 95% CI 2.84–9.67; p<0.0001) for the cenobamate 400 mg group. For safety, the percentage of patients who had at least one treatment-emergent adverse event during the double-blind treatment period was 70% (76 of 108) in the placebo group, 65% (70 of 108) in the 100 mg cenobamate group, 76% (84 of 110) in the 200 mg group, and 90% (100 of 111) in the 400 mg group. The most common adverse events (>10%) occurring more frequently in the treatment arm were somnolence, dizziness, fatigue, and headache. The most common adverse events leading to trial discontinuation occurring more frequently in the treatment arm were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo. Suicidal thoughts and behaviors were increased in the treatment arm as well. The authors stated that no clinically meaningful results were observed in changes from baseline in hematology, clinical chemistry, laboratory values, ECG studies, vital signs, or physical or neurological examinations.

Post-hoc analysis, conducted by the trial authors, showed seizure frequency in the first four weeks of treatment was reduced by a median of 45% (100 mg) and 50% (200 and 400 mg) compared with 17% in the placebo group. The mean time to first post-dose seizure was seven days in cenobamate recipients (all dosage groups; n = 293) and 6.4 days in placebo recipients (n = 97). Com-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Select Cenobamate Pharmacokinetics&lt;sup&gt;13&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
</tr>
<tr>
<td>Tmax&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>Vd&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40-50L</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
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</tbody>
</table>
| UGT Glucuronidation | Major: UGT2B7  
Minor: UGT2B4 |
| CYP Oxidation | Major: CYP2E1 & CYP2A6  
Minor: CYP2C19 & CYP3A4/5 |
| **Elimination** | |
| Renal Excretion | 87.8% |
| Fecal Excretion | 5.2% |
| Clearance | 0.45-0.63 L/h |
| T1/2<sup>c</sup> | 50-60 hours |

<sup>1</sup>Time to maximum concentration; <sup>2</sup>Volume of distribution; <sup>3</sup>Half-life
Adverse Effects and Precautions

The most common adverse effects (>10%) that were observed in clinical trials were somnolence, dizziness, fatigue, diplopia, and headache. Two patients were observed to have a hypersensitivity reaction classified as mild-moderate which resolved quickly after discontinuation. One instance of drug reaction with eosinophilia and systemic symptoms (DRESS) was noted in the study by Krauss et al. This was resolved after two months of corticosteroid use. Two other instances of DRESS were reported in other trials.

A phase 1 abuse potential study looked at 39 subjects that used sedatives recreationally. A significant number of subjects reported a euphoric sensation after administration of 200 and 400 mg of cenobamate and subjective reports of “wanting to use again” were noted. Physical dependence in clinical studies showed potential for withdrawal symptoms such as insomnia, decreased appetite, depressed mood, tremors, and amnesia. For this reason, a dose reduction over two weeks is recommended for discontinuation.

Due to the potential for QTc interval shortening, cenobamate is contraindicated in patients with familial short QTc syndrome, and caution should be used when taken with other drugs known to shorten QTc intervals. Suicidal ideation and behavior has been studied in AEDs with results showing that patients on AEDs are more likely to express these thoughts. Caution should be used in patients with clinical depression or with a known suicide risk.

Cenobamate relies on CYP enzymes for metabolism. This leads to the potential for drug interactions and caution should be used in patients on concurrent AEDs or substrates for CYP2B6 and CYP3A4/5. Cenobamate may potentially decrease plasma concentrations of oral contraceptives. Alternative forms of contraceptives should be used while taking cenobamate.
**Dosing and Administration**

Cenobamate is available in 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg tablets.13 Dose titration is recommended to reduce the potential for side effects. The recommended starting dose is 12.5 mg once daily with dose increases every two weeks up to 200 mg. The maximum dosage is 400 mg if still no clinical response. In this case, titration is recommended as 50 mg increases every two weeks until 400 mg is achieved. Cenobamate may be taken with or without food.

**Cost and Availability**

SK Life Sciences has not released an official price; however, the chief commercial officer stated in interviews that cenobamate will be priced competitively with Briviaq (brivaracetam) and Fycompa (perampanel).13 This most likely means that cenobamate will be priced between $500 and $1,000 per month. There is no prior authorization (PA) information for cenobamate, however, the newer generations require failure on other medications (ruling out compliance issues as cause of failure) and partial onset or tonic-clonic seizure diagnosis. Most likely, the PA will rule out patients that met the exclusion criteria for the initial studies. Individual insurance policies will vary in monthly copay for this drug. Cenobamate is expected to hit the market around May of 2020. The DEA is currently investigating the active ingredient for abuse potential based on published data, and cenobamate may be released as a controlled substance.13

**Clinical Implications**

While there is promising evidence for use of cenobamate in uncontrolled epilepsy, there are many weaknesses to its initial approval. Complete seizure freedom is the real goal for those suffering from epilepsy, and currently a high percentage of patients are unable to reach this goal. Cenobamate does have data to show that this may be possible for some patients.10 The bulk of this evidence, however, comes from one published phase II trial and another very similar phase II abstract. Both studies were over a short period of time, and considering refractory seizures are considered over 12 months, it is not yet known if these patients will experience seizures after the studied time period. Other, lower quality abstracts have also shown efficacy, but their lack of peer review limits their use in evaluating the true efficacy and safety of this drug.11,14,16 While older AEDs show reduction in seizure frequency, their harsh side effect profile leads to little effect on overall quality of life.9 As newer generations of epilepsy drugs hit the market, there has been a trend towards less adverse side effects, but with that comes a large price tag.17,18 Cenobamate appears to be following this trend and clinical trials show a milder side effect profile when compared to side effects such as thrombocytopenia with phenytoin or hepatotoxicity with valproic acid, though it is difficult to compare clinical trials to real world data.19,20 Therapeutic drug monitoring is also recommended for older medications such as phenytoin and valproic acid. While there is not yet any monitoring requirements for cenobamate, oxcarbazepine shares this advantage with the added advantages of being studied for longer and available at a much cheaper price.13,18 One of the biggest benefits of cenobamate is its long half-life in comparison to the variable or shorter half-lives of other AEDs with the same approval. This allows for extended protection in the case of missed doses.

Epilepsy is present disproportionately in people with low socioeconomic status, therefore high prices of newer drugs potentially limits their use in these populations. Additionally, the potential for being added as a scheduled drug may hinder its use as well. Cost-effectiveness is becoming critical in the success of new drugs, and studies showing cenobamate is more cost-effective as primary treatment, or as a second, third, or fourth additional drug versus what is currently on the market could tip the scales in its favor. In recent years, pharmacogenomics of AEDs has linked some of their adverse reactions to genetic factors. It will be a long time before such data is available for cenobamate. While epilepsy is a common disorder, there is a lack of high-quality evidence comparing head to head efficacy of AEDs. Therapy is chosen based on seizure type, cost, and adverse effect profile. Additional drugs are added as seizures continue. Therefore, it is difficult for a particular AED to have a “defined” place in therapy. Ultimately, longer studies are needed to truly assess where cenobamate will fit in. Real world evidence showing benefits in certain patient populations (kidney/liver disease, certain epileptic syndromes, etc.) would help this drug secure a spot in the epilepsy guidelines.

**Table 3 | Adverse Effects**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Cenobamate Dose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Diplopia (%)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Somnolence (%)</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness (%)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>10</td>
<td>12</td>
</tr>
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</table>

**Conclusion**

Xcopri® (cenobamate) is a new AED that was granted early FDA approval in November 2019 for treatment of uncontrolled partial seizures in adults. Xcopri® (cenobamate) is attempting to reduce the number of seizures associated with epilepsy and has shown complete seizure reduction in some patients. Further studies showing longer efficacy are needed to address the validity of these claims and to show if this drug truly has value in epilepsy treatment.

**References**

1. Fisher, R.S., Boas, W.V.E., Blume, W., et al., Epileptic seizures and epilepsy: definitions proposed by the international league against epilepsy (ILAE) and the international bureau for epilepsy (IBE). Epilepsia, 46 (2005): 470–472.


