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Drug Class Update with New Drug Evaluation: Antiepileptics

Date of Review: June 2020

Generic Name: cenobamate

Date of Last Review: January 2019
Dates of Literature Search: 08/01/18 – 02/11/20
Brand Name (Manufacturer): Xcopri® (SK Life Science, Inc.)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: To define place in therapy for a new antiepileptic drug (AED) cenobamate, recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of focal seizures in adults. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.

Research Questions:
1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. What is the effectiveness of cenobamate in reducing seizure frequency in adults with focal seizures?
3. What are the comparative harms of cenobamate in in adults with focal seizures?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which cenobamate may be beneficial or cause more harm?

Conclusions:
- Nine recently published Cochrane systematic reviews were identified for inclusion in this AED class update.[1-9] Three guidelines were published by the National Institute for Health and Clinical Guidance (NICE)[10-12] and 2 guideline updates were developed by the American Academy of Neurology (AAN) and American Epilepsy Society (AES).[13,14]
- Two Cochrane reviews provided comparative evaluations of oxcarbazepine versus phenytoin[1] and lamotrigine versus carbamazepine[2] when used as monotherapy in patients with epilepsy. Treatment failure due to adverse events occurs significantly later with oxcarbazepine than phenytoin [Hazard Ratio (HR)=0.22, 95% Confidence Interval (CI) 0.10 to 0.51, p=0.0004] based on high-quality evidence.[1] Treatment failure for any reason related to treatment (HR 0.73, 95% CI 0.64 to 0.82, P<0.00001) or due to adverse events (HR 0.54, 95% CI 0.45 to 0.65, P<0.00001) occurs earlier with carbamazepine compared to lamotrigine based on moderate-quality evidence.[2] Neither review demonstrated significant differences in efficacy with one AED compared to another AED.[1,2]
- A Cochrane meta-analysis compared topiramate to placebo as add-on treatment in adults with drug-resistant focal epilepsy.[3] Moderate-quality evidence from 11 trials demonstrated seizure freedom was more likely with topiramate compared to placebo [Relative Risk (RR) 3.67, 95% CI 1.79 to 7.54].[3] The

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included trials were of relatively short duration and provided no evidence for the long-term efficacy of topiramate.[3] High-quality evidence from 12 studies showed short-term use of add-on topiramate was associated with increased risk of treatment withdrawal due to adverse effects compared with placebo (RR 2.37, 95% CI 1.66 to 3.37).[3]

- A 2019 Cochrane review compared brivaracetam to placebo as add-on therapy for adults with drug-resistant focal epilepsy.[4] Six trials provided data to demonstrate brivaracetam is significantly more effective in reducing seizure frequency compared to placebo (RR 1.81, 95% CI 1.53 to 2.14; moderate-quality evidence).[4] The incidence of treatment withdrawals for any reason was not significantly different between brivaracetam and placebo (RR 1.27, 95% CI 0.94 to 1.76; low-quality evidence).[4] However, the analysis showed that brivaracetam was associated with a significantly higher prevalence of participants withdrawing from treatment, specifically due to adverse events (RR 1.54, 95% CI 1.02 to 2.33; low-quality evidence), compared to those receiving placebo.[4]
- A 2018 Cochrane review evaluated the efficacy and tolerability of gabapentin compared to placebo when used as add-on treatment for people with drug resistant focal epilepsy.[5] Gabapentin was significantly more efficacious than placebo in reducing seizure frequency (RR 1.89, 95% CI 1.40 to 2.55; 6 trials; moderate-quality evidence).[5] Treatment withdrawal with gabapentin was not significantly different compared with placebo (RR 1.05, 95% CI 0.74 to 1.49; moderate-quality evidence).[5] Ataxia, dizziness, fatigue, and somnolence occurred in significantly more gabapentin-treated subjects than placebo.[5] There were no significant differences in headache or nausea between gabapentin and placebo.[5]
- A 2018 Cochrane review compared the efficacy and tolerability of pregabalin with placebo or an alternative AED when used as add-on treatment for individuals with drug-resistant focal epilepsy.[6] Pregabalin was significantly more effective than placebo for reducing seizure frequency by 50% (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, low-quality evidence) and improving seizure freedom (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, moderate-quality evidence).[6] Results demonstrated efficacy for pregabalin doses from 150 mg per day to 600 mg per day, with increasing effectiveness at 600 mg doses; however issues with tolerability were noted at higher doses.[6] Participants were significantly more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, moderate-quality evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, moderate-quality evidence).[6] Compared to pregabalin, no significant differences in reduction of seizure frequency were observed by those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial), levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial).[6] No significant differences were observed between pregabalin and lamotrigine, levetiracetam, or gabapentin for treatment withdrawal due to any reason or due to adverse effects.[6]
- A 2018 Cochrane review evaluated the efficacy and tolerability of rufinamide for people with refractory epilepsy.[7] Rufinamide was significantly more effective than placebo in reducing seizure frequency by at least 50%, when added to conventional AEDs in people with refractory focal epilepsy (RR 1.79, 95% CI 1.44 to 2.22; 6 trials; moderate-quality evidence).[7] Treatment withdrawal (for any reason and due to adverse effects) was significantly more likely with rufinamide than placebo (RR 1.83, 95% CI 1.45 to 2.31; 6 trials; moderate-quality evidence).[7] Adverse effects associated with rufinamide included headache, dizziness, somnolence, vomiting, nausea, fatigue and diplopia.[7]
- A 2019 Cochrane review evaluated clinical trials of pregabalin compared to placebo in treatment of neuropathic pain in adults.[8] Moderate-quality evidence showed pregabalin reduces pain intensity by 50% in post-herpetic neuralgia compared to placebo (pregabalin 32% vs. placebo 13%; RR 2.5, 95% CI 1.9 to 3.4); painful diabetic neuropathy (31% vs. 24%; RR 1.3, 95% CI 1.2 to 1.5); and mixed or unclassified post-traumatic neuropathic pain (34% vs. 20%; RR 1.5 95% CI 1.2 to 1.9), and absence of efficacy in HIV neuropathy.[8] Evidence of pregabalin efficacy in central neuropathic pain is inadequate.[8] When all neuropathic pain studies were analyzed, serious adverse events were no more common with placebo than with pregabalin 300 mg (3.1% vs. 2.6%; RR 1.2, 95% CI 0.8 to 1.7; 17 trials; high-quality evidence) or pregabalin 600 mg (3.4% vs. 3.4%; RR 1.1, 95% CI 0.8 to 1.5; 16 studies; high-quality evidence).[8]
- A 2019 Cochrane review assessed the efficacy and tolerability of valproate for acute manic episodes in bipolar disorder compared to placebo, alternative pharmacological treatments, or combination pharmacological treatments.[9] High-quality evidence shows valproate is an efficacious treatment for acute mania in adults when compared to placebo (45% valproate vs. 29% placebo, Odds Ratio (OR) 2.05, 95% CI 1.32 to 3.20; 4 studies).[9] In contrast, there is no evidence of a difference in efficacy between valproate and placebo for treating acute mania for children and adolescents.[9] Low-quality evidence shows

valproate has little difference in response rate than olanzapine in adults (38% valproate vs. 44%, olanzapine OR 0.77, 95% CI 0.48 to 1.25; 2 studies).[9] Moderate-quality evidence found that more participants receiving valproate experienced adverse events compared to placebo (83% valproate vs. 75% placebo, OR 1.63, 95% CI 1.13 to 2.36; 3 studies).[9] Low-quality evidence found there may be little or no difference in tolerability between valproate and lithium (78% valproate vs. 86%, lithium OR 0.61, 95% CI 0.25 to 1.50; 2 studies).[9]

- In February 2020, NICE strengthened guidance to avoid valproate in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable.[10] Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and may only take valproate if they have a pregnancy prevention program in place, in line with the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on valproate.[10] The risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child should be discussed with all women of childbearing potential.[10]
- Recommendations for treatment of seizures associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) with cannabidiol and clobazam were published by NICE in December 2019.[11,12] Cannabidiol with clobazam is recommended as an option for treating seizures associated with DS or LGS in people aged 2 years and older, with mandatory check of frequency of convulsive seizures every 6 months.[11,12] Cannabidiol should be stopped if seizure frequency has not fallen by at least 30% compared with the 6 months before starting treatment.[11,12]
- In 2018, The AAN and AES published a 2-part guideline update focused on the efficacy and tolerability of recently approved AEDs.[13,14] Part 1 evaluated evidence for treatment of new-onset epilepsy with newer AEDs.[13] In adults with new-onset focal epilepsy, lamotrigine should be considered to decrease seizure frequency.[13] Levetiracetam and zonisamide may be considered as alternatives to decrease seizure frequency in adults with new-onset focal epilepsy.[13] In adults 60 years and older, lamotrigine should be considered in decreasing seizure frequency in patients with new-onset focal epilepsy.[13] Gabapentin may be considered in decreasing seizure frequency in patients with new-onset focal epilepsy.[13] Unless there are compelling adverse effect–related concerns, ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency when treating absence seizures in childhood absence epilepsy.[13]
- Part 2 of the AAN/AES guidance evaluated evidence for treatment-resistant epilepsy with newer AEDs.[14] AED selection depends on seizure/syndrome type, patient age, concomitant medications, and AED tolerability, safety, and efficacy.[14] The following AEDs are established as effective to reduce seizure frequency: immediate-release pregabalin and perampanel for treatment-resistant adult focal epilepsy ; vigabatrin for treatment-resistant adult focal epilepsy (not first-line treatment); and rufinamide for LGS (add-on therapy).[14]

Cenobamate

- The safety and efficacy of adjunctive oral cenobamate in treating adults with uncontrolled focal seizures was evaluated in a moderate-quality phase 2 randomized controlled trial (RCT).[15] Adult patients with treatment-resistant focal seizures (n=437) taking 1 to 3 AEDs were randomly assigned (1:1:1:1) to once daily oral cenobamate 100 mg, 200 mg, 400 mg, or placebo.[15] The primary outcome was reduction in 28 day focal seizure frequency from baseline to the end of the double-blind treatment phase (12 weeks). Moderate-quality data from this trial demonstrates adjunctive cenobamate significantly reduces focal seizure frequency compared to placebo.[15] Median percentage reductions in seizure frequency over 12 weeks from baseline were 24.0% [Interquartile Range (IQR) 45.0 to 7.0%] for the placebo group compared with 35.5% (IQR 62.5 to 5.0%; p=0.0071 vs. placebo) for the 100 mg dose group, and 55.0% for the 200 mg and 400 mg dose groups (IQR 73.0 to 23.0% and 85.0 to 28.0%, respectively, P<0.0001 vs. placebo for both doses).[15]
- Treatment-emergent adverse events identified in the trial led to discontinuation in 5% of patients in the placebo group, 10% in the 100 mg dose group, 14% in the 200 mg dose group, and 20% in the 400 mg dose group.[15] The most common AEs reported in all the cenobamate trials which occurred in greater than 10% of patients were somnolence, dizziness, fatigue, and diplopia.[16]
- Limitations of this study include the short study duration and the potential effect of concomitant AEDs. In addition, type of seizure and seizure frequency were self-recorded by the subjects, which could contribute to detection bias.[15]

Recommendations:

- Designate cenobamate as non-preferred drug on the Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan (PMPDP).
- Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

Two new AEDs, cannabidiol and stiripentol, were reviewed at the January 2019 Pharmacy and Therapeutics (P and T) Committee meeting. After discussion, the committee recommended the implementation of prior authorization (PA) criteria to ensure medically appropriate utilization of cannabidiol and stiripentol. The preferred oral and rectal AEDs included on the Oregon Medicaid FFS (Fee-For-Service) Preferred Drug List (PDL) are: carbamazepine, diazepam, divalproex, ethosuximide, ethotoin, gabapentin, lacosamide, levetiracetam, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproic acid, and zonisamide. Lamotrigine is classified as a voluntary medication due to its utilization in mental health treatment. Non-preferred AEDs are listed in **Appendix 1**. The utilization of clobazam, pregabalin, and topiramate is guided by prior authorization (PA) criteria to ensure they are prescribed for indications supported by the medial literature. The PA criteria for cannabidiol, clobazam, pregabalin, stiripentol, and topiramate are presented in **Appendix 4.**

Medicaid Fee-for-Service Utilization

A review of pharmacy AED claims paid 7/1/19 through 9/30/19 provided an overview of Medicaid Fee for Service (FFS) utilization in the third quarter of 2019. Ninety-seven percent of the claims were for preferred or voluntary agents in the AED class. The most frequently requested preferred agent was lamotrigine with over 60% of claims, followed by divalproex (20%) and gabapentin (4%). The most requested non-preferred AED was pregabalin followed by clobazam.

Background:

In 2014, the International League Against Epilepsy (ILAE) defined epilepsy as a disease of the brain, diagnosis of which requires: (a) at least two unprovoked seizures occurring more than 24 hours apart; (b) one unprovoked seizure with at least 60% probability for further seizures occurring over the next 10 years, or (c) the diagnosis of an epilepsy syndrome.[17] The causes of epilepsy vary and are identified in only about 30% of people with the disorder.[18] Worldwide, an estimated 65 million people have epilepsy.[19] In the United States, approximately 150,000 adults present annually with an unprovoked first seizure.[20] The incidence of epilepsy has a bimodal distribution with the highest risk in infants and older age groups.[21] Common risk factors include premature birth; complicated febrile seizures; infections, such as meningitis or encephalitis; head trauma; or family history of epilepsy or neurologic illnesses.[18] Causes of epilepsy may include structural lesions, abnormalities of neuronal migration, and fetal intracranial hemorrhage.[18] Other acquired lesions can serve as seizure foci, including benign and malignant intracranial or extra-axial tumors, abscesses, cysts, hemorrhagic lesions, or strokes.[18] Systemic illnesses, such as HIV infection and malaria, can also lead to chronic epilepsy.[18]

In 2017, ILAE updated the classification of seizure types based on the initial manifestation of the seizure as generalized, focal, or unknown (if seizure onset is either missed or obscured).[22] Of note, the terms simple partial, complex partial, and secondarily generalized tonic-clonic have been eliminated, since they were difficult to define pragmatically and were often used incorrectly.[22] Generalized seizures are generally distributed bilaterally to both cerebral hemispheres and are further classified as motor (tonic-clonic) or non-motor (absence) seizures.[22] Focal seizures originate within networks limited to one cerebral hemisphere. Focal seizures are further subdivided based on level of patient awareness (aware or impaired awareness).[22] Additionally, focal seizures are subgrouped into motor and non-motor seizures, based on signs and symptoms at onset.[22] Additional descriptors for both generalized and focal seizures may be added based on specific motor or non-motor symptoms.[22]

Antiepileptic drugs work by stabilizing cellular mechanisms that prevent spontaneous neuronal depolarization.[18] The exact mechanisms by which various medications influence this function include interaction through sodium, calcium, or potassium channels or effects on neurotransmitters such as gamma-aminobutyric acid (GABA) or glutamate.[18] Drug selection is based upon seizure type, the adverse effect profile, childbearing potential of the patient, co-prescribed medications, and patient preference. Approximately half of newly diagnosed patients with epilepsy are successfully treated with the first AED; however, treatment failure and drug intolerance can occur. Monotherapy is more likely to promote compliance, reduce potential for drug interactions, and is less costly but may not keep a patient seizure-free. For approximately 70% of people with epilepsy, seizures can be controlled with a single antiepileptic drug.[23] The remaining 30% of individuals experience refractory or drug-resistant seizures, which often require combinations of AEDs or alternative treatments such as surgery.[24] According to a 2010 ILAE task force, drug-resistant epilepsy may be defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[25]

The pharmacologic management of patients with epilepsy is focused on 3 main goals: 1) controlling seizures, 2) avoiding adverse effects, and 3) maintaining or restoring quality of life.[26] The NICE epilepsy guidelines provide detailed prescribing considerations for AEDs.[27] According to the 2012 NICE guidelines, first-line agents for treatment of focal seizures include carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and valproate.[27] Second-line agents include clobazam, gabapentin, and topiramate.[27] For generalized motor seizures first-line options include valproate, lamotrigine, carbamazepine, or oxcarbazepine.[27] Clobazam, levetiracetam, or topiramate are second-line agents if first-line agents are ineffective or not tolerated.[27] If non-motor seizures are present, then carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin are not recommended as they can precipitate or aggravate seizures.[27] Per the 2012 NICE guidance, ethosuximide, valproate, and lamotrigine are the recommended agents to treat absence seizures.[27] Most of the newer AEDs have been developed in an effort to improve safety and tolerability.

Indications for immediate AED treatment are based largely on estimations of an individual's risk of a seizure recurrence.[28] Evidence indicates that immediate AED therapy is likely to reduce seizure recurrence risk for individuals with an unprovoked first seizure, particularly within the first 2 years.[28] Such seizure recurrence prevention, even in the short term, may be important, with potentially greater implications for adults than for children.[28] For adults, seizure recurrences may cause such serious psychological and social consequences as loss of driving privileges and limitations on employment.[28] Although individual seizure recurrences pose some risk for physical harm and even death, there is no evidence that immediate AED treatment reduces that risk or improves quality of life (QOL).[28] The issue of exactly how to use complicated risk data of recurrences and seizure remission to guide management is a question that warrants further research and clarification.[28]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane Meta-Analyses of Individual Participant Data

A series of Cochrane reviews evaluating pair-wise monotherapy comparisons of carbamazepine, lamotrigine, topiramate, oxcarbazepine, phenobarbital, phenytoin and valproate in treating epilepsy were updated in 2018 and 2019.[1,2,29-33] Each of these updates compiled a meta-analysis of individual participant data (IPD), in which the raw individual level data for each study were obtained from the investigators and used for synthesis of the meta-analysis.[34] Traditional meta-analysis methods involve combining quantitative evidence from related studies to evaluate outcomes. The goal of IPD meta-analysis is to summarize the raw data on a specific clinical question from multiple related studies.[34] IPD analyses are time consuming to generate because the original investigators must be contacted to ask if they will share their raw data for the report. Only the updates that were based on moderate to high quality evidence will be described in detail for this class update. Five separate updates evaluated carbamazepine with phenobarbital,[29] carbamazepine with phenytoin,[30] phenytoin with valproate,[31] topiramate with carbamazepine,[32] and phenobarbital with phenytoin,[33] but the recently published trials included in these updates were imprecise and may have misclassified seizure type, so the methodological quality of the evidence was rated as low by the Cochrane reviewers. Therefore, they are not included in this summary. Two IPD meta-analyses based on moderate quality evidence are summarized below.

Oxcarbazepine versus Phenytoin

A 2018 Cochrane review updated a previous 2013 publication comparing oxcarbazepine to phenytoin monotherapy in people with focal onset seizures or generalized motor seizures using the IPD methodology.[1] Literature was searched through August 2018. Evidence from 3 studies (n=517) met inclusion criteria.[1] The results of this review are applicable mainly to individuals with focal onset seizures; 70% of included individuals experienced seizures of this type at baseline.[1] The primary outcome was time to treatment failure (retention time). Secondary outcomes included remission, time to first seizure with oxcarbazepine compared to phenytoin, and incidence of adverse events. The 2 studies included in IPD meta-analysis were generally of good methodological quality but the design of the studies may have biased the results for some of the secondary outcomes (time to first seizure post-randomization, time to six-month and 12-month remission) as seizure recurrence data were not collected following treatment failure or withdrawal from the study.[1]

Data from 2 trials (n=480) were combined to assess time to treatment failure. For this outcome, a HR less than one indicates a clinical advantage for oxcarbazepine.[1] Time to treatment failure for any reason related to treatment was not statistically significant when oxcarbazepine was compared to phenytoin (pooled HR 0.78, 95% CI 0.53 to 1.14, P=0.20, moderate-quality evidence).[1] Treatment failure due to adverse events occurred later with oxcarbazepine than phenytoin (HR=0.22, 95% CI 0.10 to 0.51, p=0.0004, high-quality evidence).[1] Time to treatment failure due to lack of efficacy showed no clear difference between oxcarbazepine and phenytoin (HR=1.17, 95% CI 0.31 to 4.35, p=0.82, moderate-quality evidence).[1] The most common adverse events reported in more than 10% of participants on either drug were somnolence (28% of total participants, with similar rates for both drugs), headache (15% of total participants, with similar rates for both drugs), dizziness [14.5% of total participants, reported by more participants on phenytoin (18%) than oxcarbazepine (11%)] and gum hyperplasia [reported by substantially more participants on phenytoin (18%) than oxcarbazepine (2%)]; confidence intervals and statistical significance were not provided for adverse event rates.[1] In summary, high-quality evidence provided by this review indicates that treatment failure due to adverse events occurs significantly later with oxcarbazepine than phenytoin.[1]

Lamotrigine versus Carbamazepine

A 2018 Cochrane review updated a previous 2006 publication comparing lamotrigine to carbamazepine monotherapy in people with focal onset seizures or generalized motor seizures using the IPD methodology.[2] Literature was searched through February 2018. Fourteen trials met inclusion criteria. Individual participant data were available for 2572 participants out of 3787 eligible individuals from 9 out of 14 trials.[2] For remission outcomes, a HR of less than one indicated an advantage for carbamazepine; and for first seizure and treatment failure outcomes, a HR of less than one indicated an advantage for lamotrigine.[2]

Of 3768 participants that had reasons for treatment failure or withdrawal, 38% of all participants prematurely withdrew from treatment (33% of participants randomized to lamotrigine and 44% participants randomized to carbamazepine).[2] Eighty-six percent of total treatment failures were in subjects who withdrew for reasons related to the allocated drug: 86% of treatment failures for lamotrigine and 87% of treatment failures for carbamazepine.[2] The most common treatment-related reason for treatment failure was adverse events noted in 44% of total treatment failures. Thirty-six percent of total treatment failures were for lamotrigine and 52% of total treatment failures for carbamazepine.[2] Time to treatment failure for any reason was HR 0.73 (95% CI 0.64 to 0.82, P<0.00001, I^2=13% moderate-quality evidence, n=2569, 9 trials) indicating a statistically significant advantage with lamotrigine versus carbamazepine.[2] For time to treatment failure due to adverse events, the overall pooled HR was 0.54 (95% CI 0.45 to 0.65, P<0.00001, moderate-quality evidence) indicating a statistically significant advantage with lamotrigine.[2] Considering time to treatment failure due to lack of efficacy, 1874 participants provided IPD from 5 trials; no participants withdrew from one or both of the drugs due to lack of efficacy in four trials.[2] The overall pooled HR was 1.03 (95% CI 0.75 to 1.41, P=0.86, I^2=0% moderate-quality evidence) indicating no statistically significant difference between lamotrigine and carbamazepine.[2] In summary, moderate quality evidence indicates that treatment failure for any reason related to treatment or due to adverse events occurs significantly earlier with carbamazepine compared to lamotrigine.[2]

Cochrane: Topiramate Add-On Therapy for Drug-Resistant Epilepsy

A 2019 Cochrane review updated a previous review focused on topiramate efficacy and tolerability as add-on therapy for people with drug-resistant focal epilepsy.[3] The literature search was completed through July 2018. Twelve trials (n=1650) met inclusion criteria. Topiramate doses ranged from 200 mg per day to 1000 mg per day.[3] The primary outcome was the proportion of people with a 50% or greater reduction in seizure frequency compared to baseline.[3] Secondary outcomes included the proportion of people with complete seizure cessation and treatment withdrawal for any reason.[3] Ten RCTs compared topiramate to placebo in adults (aged 18 to 75 years), one RCT compared topiramate to placebo in children (aged 1 to 16 years), and one RCT compared topiramate to placebo in elderly patients (aged over 65 years). In all trials, participants were eligible if they experienced a minimum number of focal seizures (range 3 to 12 seizures) and were currently taking more than one AED.[3] Treatment periods ranged from 11 to 19 weeks. Eleven studies included in the meta-analysis were rated as having low risk of bias.[3] The RCT conducted in elderly patients had an unclear risk of bias due to insufficient descriptions of allocation concealment, blinding of investigators, and blinding for outcome assessment.[3]

Response to therapy (50% or greater reduction in seizure frequency) was more likely with topiramate compared to placebo (RR 4.36, 95% CI 2.24 to 8.50; 11 studies, I^2=0; high-certainty evidence).[3] Seizure freedom was also more likely with topiramate compared to placebo (RR 3.67, 95% CI 1.79 to 7.54; 8 studies; moderate-certainty evidence).[3] However, participants were more likely to withdraw from the study early when assigned to topiramate than placebo (RR 2.37, 95% CI 1.66 to 3.37; 12 studies; high-certainty evidence).[3] Specifically, add-on topiramate was associated with a higher incidence of the following adverse effects compared to placebo: ataxia (RR 2.29, 95% CI 1.10 to 4.77, P=0.003), concentration difficulties (RR 7.81, 95% CI 2.08 to 29.29, P<0.001), dizziness (RR 1.52, 95% CI 1.07 to 2.16, P=0.002), fatigue (RR 2.08, 95% CI 1.37 to 3.15, P<0.001) , paresthesia (RR 3.65, 95% CI 1.58 to 8.39, P<0.001), somnolence (RR 2.44, 95% CI 1.61 to 3.68, P<0.001), speech difficulty (RR 3.37, 95% CI 0.80 to 14.13, P=0.03), and weight loss (RR 3.99, 95% CI 1.82 to 8.72, P<0.001).[3]

In summary, topiramate is efficacious as add-on treatment for drug-resistant focal epilepsy as it is more effective than placebo at reducing seizure frequency in adults.[3] However, the trials reviewed were of relatively short duration and provided no evidence for the long-term efficacy.[3] Short-term use of add-on topiramate was shown to be associated with increased risk of adverse events compared with placebo.[3]

Cochrane: Brivaracetam Add-On Therapy for Drug-Resistant Epilepsy

A 2019 Cochrane review evaluated the efficacy and tolerability of brivaracetam when used as add-on treatment for people with drug-resistant epilepsy.[35] The literature search was conducted through October 2018. Six double-blind, placebo-controlled RCTs representing 2411 participants met inclusion criteria.[35] One study included participants with both focal and generalized onset seizures; the other 5 trials included participants with focal onset seizures only.[35] All 6 studies included adult participants between 16 and 80 years of age, and treatment periods ranged from 7 to 16 weeks.[35] Two studies were judged to have low risk of bias and 4 studies had unclear risk of bias.[35] One study failed to provide details on the method used for allocation concealment, and one did not report all outcomes prespecified in the trial protocol.[35] One study did not describe how blinding was maintained, and another noted discrepancies in reporting.[35] The primary outcome was the proportion of individuals with a 50% or greater reduction in seizure frequency compared to baseline.[35] Secondary outcomes included proportion of patients with complete seizure cessation, treatment withdrawal, and adverse effects.

Participants who received brivaracetam were more likely to achieve a 50% or greater reduction in seizure frequency, compared to those who received placebo (RR 1.81, 95% CI 1.53 to 2.14, I^2 not reported, moderate-quality evidence.)[35] Participants who received brivaracetam were more likely to experience seizure freedom than those on placebo (RR 5.89, 95% CI 2.30 to 15.13; I^2=0%, moderate-quality evidence).[35] No difference was found in the proportion of participants who withdrew from treatment between those assigned to brivaracetam versus placebo (RR 1.27, 95% CI 0.94 to 1.74, I^2 not reported, low-quality evidence).[35] In contrast, those who received brivaracetam were more likely to withdraw from treatment due to adverse events (RR 1.54, 95% CI 1.02 to 2.33; low-quality evidence), compared to placebo.[35]

In summary, brivaracetam, when used as add-on therapy for adults patients with drug-resistant focal epilepsy, is effective in reducing seizure frequency compared to placebo.[35] The incidence of treatment withdrawals for any reason was not significantly different between brivaracetam and placebo.[35] However, add-on brivaracetam was associated with a greater proportion of treatment withdrawals due to adverse events compared with placebo.[35] None of the studies included participants under the age of 16, and all studies were of short duration.[35]

Gabapentin Add-on Therapy for Drug-Resistant Focal Epilepsy

A 2018 Cochrane review updated a previously published 2013 version to evaluate the efficacy and tolerability of gabapentin when used as add-on treatment for people with drug resistant focal epilepsy.[5] The literature search was conducted through March 2018. Data from 6 trials were included in the meta-analyses of 1206 randomized participants.[5] Overall, the studies were rated at low to unclear risk of bias due to incomplete information. The overall quality of evidence was judged as low to moderate due to potential attrition bias resulting from missing outcome data and imprecise results with wide confidence intervals.[5]

Reduction in seizure frequency was more likely with gabapentin compared to placebo (RR 1.89, 95% CI 1.40 to 2.55; 6 trials, 1206 participants; moderate-quality evidence).[5] No significant differences in proportion of patients withdrawing from treatment between gabapentin and placebo were observed (RR 1.05, 95% CI 0.74 to 1.49; moderate-quality evidence).[5] Adverse effects higher with gabapentin than placebo for the following: ataxia 2.01 (99% CI 0.98 to 4.11; 3 studies, 787 participants; low-quality evidence), dizziness 2.43 (99% CI 1.44 to 4.12; 6 studies, 1206 participants; moderate-quality evidence), fatigue 1.95 (99% CI 0.99 to 3.82; 5 studies, 1161 participants; low-quality evidence) and somnolence 1.93 (99% CI 1.22 to 3.06; 6 studies, 1206 participants; moderate-quality evidence).[5] No differences were noted between gabapentin and placebo for headache (RR 0.79, 99% CI 0.46 to 1.35; 6 studies, 1206 participants; moderate-quality evidence) or nausea (RR 0.95, 99% CI 0.52 to 1.73; 4 trials, 1034 participants; moderate-quality evidence).[5]

In summary, gabapentin efficacious compared to placebo when studied as an add-on treatment in patients with drug-resistant focal epilepsy.[5] However, the trials reviewed were of relatively short duration and provide no evidence for the long-term efficacy of gabapentin beyond 3 months.[5] The results cannot be extrapolated to monotherapy or to people with other epilepsy types.[5]

Cochrane: Pregabalin Add-on Therapy for Drug-Resistant Focal Epilepsy

A 2018 Cochrane review updated a previously published 2014 version to evaluate the efficacy and tolerability of pregabalin when used as add-on treatment for individuals with drug resistant focal epilepsy.[6] Literature was searched through July 2018. Nine industry-sponsored randomized controlled trials (3327 participants) are included in the update.[6] Three RCTs were recently identified and analyzed with the additional 6 RCTs identified in the 2014 review.[6]

For the primary outcome, participants randomized to pregabalin were more likely to attain a 50% or greater reduction in seizure frequency compared to placebo (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, 2193 participants, low-quality evidence).[6] The odds of response doubled with an increase in pregabalin dose from 300 mg per day to 600 mg per day (OR 1.99, 95% CI 1.74 to 2.28), indicating a dose-response relationship.[6] More patients were seizure-free on pregabalin compared to placebo (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, 1125 participants, moderate-quality evidence).[6] However, patients were more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, 2193 participants, moderate-quality evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, 2193 participants, moderate-quality evidence).[6] Analyses pooling across doses (50 mg per day to 600 mg per day immediate- and controlled-release pregabalin) indicated that ataxia (RR 3.90, 99% CI 2.05 to 7.42); dizziness (RR 3.15, 99% CI 2.23 to 4.44); fatigue (RR 1.34, 99% CI 0.93 to 1.94); somnolence (RR 2.15, 99% CI 1.50 to 3.09); and weight gain (RR 5.02, 99% CI 2.49 to 10.10) were all more prevalent in participants randomized to pregabalin compared to placebo.[6] Incidence of nausea did not differ between pregabalin and placebo groups (RR 1.20, 99% CI 0.56 to 2.58).[6] In contrast, participants randomized to pregabalin were less likely to experience headache compared to those randomized to placebo (RR 0.63, 99% CI 0.42 to 0.93).[6]

Three trials compared pregabalin to active-control drugs: lamotrigine, levetiracetam, and gabapentin.[6] Compared to pregabalin, no differences in reduction of seizure frequency were observed with those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial, 293 participants), levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial, 509 participants) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial, 484 participants).[6] No differences were observed between pregabalin and lamotrigine (RR 1.07, 95% CI 0.75 to 1.52), levetiracetam (RR 1.03, 95% CI 0.71 to 1.49), or gabapentin (RR 0.78, 95% CI 0.57 to 1.07) for treatment withdrawal due to any reason or due to adverse effects (pregabalin vs. lamotrigine: RR 0.89, 95% CI 0.53 to 1.48; vs. levetiracetam: RR 1.29, 95% CI 0.66 to 2.54; vs. gabapentin: RR 1.07, 95% CI 0.54 to 2.11).[6]

Pregabalin, when used as an add-on drug for treatment-resistant focal epilepsy, is more effective than placebo at producing a 50% or greater seizure reduction and seizure freedom. Results demonstrated efficacy for doses from 150 to 600 mg per day, with increasing effectiveness at 600 mg per day; however, issues with tolerability were noted at higher doses.[6] The evidence suggests that there is no significant difference in efficacy and harms between pregabalin and some of the other AEDs gabapentin, levetiracetam, and lamotrigine.[6] The trials included in this review were of short duration.[6]

Cochrane: Rufinamide Add-on Therapy for Refractory Epilepsy

A 2018 Cochrane review evaluated the efficacy and tolerability of add-on rufinamide for people with refractory epilepsy.[7] The literature search was conducted through October 2017. The review included 6 trials, representing 1759 participants.[7] Four trials (1563 participants) included people with uncontrolled focal seizures. Two trials (196 participants) included patients with LGS. Overall, the age of the adults ranged from 18 to 80 years and the age of the infants ranged from 4 to 16 years.[7] Baseline phase ranged from 28 to 56 days and double-blind phases from 84 to 96 days.[7] Five of the 6 included trials described adequate

methods of concealment of randomization and only 3 trials adequately described blinding.[7] Overall, the evidence was assessed as moderate to low quality, due to potential risk of bias from some studies contributing to the analysis and wide CIs.

Rufinamide added to current AED treatment was more effective than placebo added to current AED in reducing seizure frequency by at least 50%, when used in people with refractory focal epilepsy (RR 1.79, 95% CI 1.44 to 2.22; 6 RCTs; moderate-quality evidence).[7] Treatment withdrawal (for any reason and due to adverse effects) was more likely with the rufinamide group than placebo (RR 1.83, 95% CI 1.45 to 2.31; 6 RCTs; moderate-quality evidence).[7] Adverse events associated with rufinamide included: headache 1.36 (95% Cl 1.08 to 1.69; 3 RCTs; high-quality evidence); dizziness 2.52 (95% Cl 1.90 to 3.34; 3 RCTs; moderate-quality evidence); somnolence 1.94 (95% Cl 1.44 to 2.61; 6 RCTs; moderate-quality evidence); vomiting 2.95 (95% Cl 1.80 to 4.82; 4 RCTs; low-quality evidence); nausea 1.87 (95% Cl 1.33 to 2.64; 3 RCTs; moderate-quality evidence); fatigue 1.46 (95% Cl 1.08 to 1.97; 3 RCTs; moderate-quality evidence); and diplopia 4.60 (95% Cl 2.53 to 8.38; 3 RCTs; low-quality evidence).[7] There was no important heterogeneity between studies for any of the outcomes.

In people with drug-resistant focal epilepsy, rufinamide when used as an add-on treatment was effective in reducing seizure frequency but with several adverse effects.[7] The trials reviewed were of relatively short duration and provided no evidence for the long-term use of rufinamide.[7]

Cochrane: Pregabalin for Neuropathic Pain

A 2019 Cochrane review updated a previous 2009 Cochrane publication focused on pregabalin for acute and chronic pain in adults.[8] For this update, the literature search was narrowed to evaluate clinical trials that used pregabalin to treat neuropathic pain in adults.[8] Literature was searched through August 2018. Thirty-one new studies with 8045 participants were identified.[8] Studies lasted 2 to 16 weeks. A diagnosis of post-herpetic neuralgia, painful diabetic neuropathy, or mixed neuropathic pain were the most frequent indications (85% of participants).[8]

Post-Herpetic Neuralgia

In subjects with post-herpetic neuralgia, more participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo [50% vs. 25%; RR 2.1 (95% CI 1.6 to 2.6); NNT 4 (95% CI 3.0 to 5.6); 3 studies, 589 participants, moderate-quality evidence], and more subjects had at least 50% pain intensity reduction [32% vs 13%; RR 2.5 (95% CI 1.9 to 3.4); NNT 6 (95% CI 3.9 to 8.1); 4 studies, 713 participants, moderate-quality evidence].[8] More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [62% vs. 24%; RR 2.5 (95% CI 2.0 to 3.2); NNT 3 (95% CI 2.2 to 3.7); 3 studies, 537 participants, moderate-quality evidence], and more had at least 50% pain intensity reduction [41% vs. 15%; RR 2.7 (95% CI 2.0 to 3.5); NNT 4 (95% CI 3.1 to 5.5); 4 studies, 732 participants, moderate-quality evidence].[8] Somnolence and dizziness were more common with pregabalin than with placebo based on moderate-quality evidence (somnolence: 300 mg 16% vs. 5.5% and 600 mg 25% vs. 5.8%; dizziness: 300 mg 29% vs. 8.1% and 600 mg 35% vs. 8.8%, respectively).[8]

Painful Diabetic Neuropathy

In patients with diabetic neuropathy, more participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo [47% vs. 42%; RR 1.1 (95% CI 1.01 to 1.2); NNT 22 (95% CI 12 to 200); 8 studies, 2320 participants, moderate-quality evidence], more had at least 50% pain intensity reduction [31% vs. 24%; RR 1.3 (95% CI 1.2 to 1.5); NNT 22 (95% CI 12 to 200); 11 studies, 2931 participants, moderate-quality evidence].[8] More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [63% vs. 52%; RR 1.2 (95% CI 1.04 to 1.4); NNT 10 (95% CI 5.5 to 41); 2 studies, 611 participants, low-quality evidence], and more had at least 50% pain intensity reduction [41% vs. 28%; RR 1.4 (95% CI 1.2 to 1.7); NNT 8 (95% CI 5.4 to 14); 5 studies, 1015 participants, low-quality evidence].[8] Somnolence and dizziness were more common with pregabalin than with placebo based on moderate-quality evidence (somnolence: 300 mg 11% vs. 3.1% and 600 mg 15% vs. 4.5%; dizziness: 300 mg 13% vs. 3.8% and 600 mg 22% vs. 4.4%.[8]

Mixed or Unclassified Post-Traumatic Neuropathic Pain
For mixed or unclassified post-traumatic neuropathic pain, more participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [48% vs. 36%; RR 1.2 (1.1 to 1.4); NNT 9 (95% CI 5.7 to 15); 4 studies, 1367 participants, low-quality evidence], and more had at least 50% pain intensity reduction [34% vs. 20%; RR 1.5 (95% CI 1.2 to 1.9); NNT 8 (95% CI 5.4 to 11); 4 studies, 1367 participants, moderate-quality evidence].[8] Somnolence (12% vs. 3.9%) and dizziness (23% vs. 6.2%) were more common with pregabalin.[8]

Central Neuropathic Pain
In subjects with central neuropathic pain, more participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [44% vs. 28%; RR 1.6 (95% CI 1.3 to 2.0); NNT 6 (95% CI 4.1 to 11); 3 studies, 562 participants, low-quality evidence] and at least 50% pain intensity reduction [26% vs. 15%; RR 1.7 (95% CI 1.2 to 2.3); NNT 10 (95% CI 6.0 to 28); 3 studies, 562 participants, low-quality evidence].[8] Somnolence (32% vs. 11%) and dizziness (23% vs. 8.6%) were more common with pregabalin than placebo, respectively.[8]

Other Neuropathic Pain Conditions
Studies show no evidence of benefit for 600 mg pregabalin in HIV neuropathy (2 studies, 674 participants, moderate-quality evidence) and limited evidence of benefit in neuropathic back pain or sciatica, neuropathic cancer pain, or polyneuropathy.[8]

In summary, moderate quality evidence demonstrated efficacy with pregabalin at reducing pain intensity by 50% in post-herpetic neuralgia, painful diabetic neuropathy, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy. Evidence of efficacy in central neuropathic pain was inadequate.[8] When all neuropathic pain studies were analyzed in a meta-analysis, serious adverse events were no more common with placebo than with pregabalin 300 mg (3.1% vs. 2.6%; RR 1.2, 95% CI 0.8 to 1.7; 17 studies, 4112 participants, high-quality evidence) or pregabalin 600 mg (3.4% vs. 3.4%; RR 1.1, 95% CI 0.8 to 1.5; 16 studies, 3995 participants, high-quality evidence).[8]

Cochrane: Valproate for Acute Mania
A 2019 Cochrane review assessed the efficacy and tolerability of valproate for acute manic episodes in bipolar disorder compared to placebo or alternative pharmacological treatments in pediatric, adolescent and adult populations.[9] Twenty-five trials (3252 participants) compared valproate with either placebo or alternative anti-manic treatments (lithium, olanzapine, risperidone) to alleviate the symptoms of acute mania.[9] The primary outcome to assess efficacy was response rate.[9] The primary outcome to assess tolerability was the number of participants with any adverse effect.[9] The majority of studies focused on adult men and women (aged 18 and above), were conducted in inpatient settings and completed in the US.[9] Five studies in this review focused on children and adolescents (aged 18 and under), expanding the age range of the review from 3 to 82 years.[9] Nine studies included data collected outside the US, namely Iran (4 studies), India (3 studies), China (1 study), or across several countries (1 study).[9]

Valproate induced a slightly higher response in alleviating manic symptoms in adults compared to placebo (45% vs. 29%, OR 2.05, 95% CI 1.32 to 3.20; 4 studies, 869 participants) based on high quality evidence.[9] No difference in response rates were found between valproate and lithium (56% vs. 62%, OR 0.80, 95% CI 0.48 to 1.35; 3 studies, 356 participants) based on moderate-quality evidence.[9] In addition no difference in response rate was found between valproate and olanzapine (38% vs. 44%, OR 0.77, 95% CI 0.48 to 1.25; 2 studies, 667 participants) based on low-quality evidence.[9]

In the children and adolescent population, differences in response rates between valproate and placebo was uncertain (23% vs. 22%, OR 1.11, 95% CI 0.51 to 2.38; 1 study, 151 participants, low-quality evidence).[9] Response rates of patients who received valproate were lower compared to risperidone (23% vs. 66%, OR

0.16, 95% CI 0.08 to 0.29; 1 study, 197 participants) based on low-quality evidence.[9] The evidence regarding any difference in response rates between valproate and lithium was uncertain (23% vs. 34%, OR 0.57, 95% CI 0.31 to 1.07; 1 study, 197 participants, low-quality evidence).[9]

More participants who received valproate experienced an adverse event compared to placebo (83% vs. 75%, OR 1.63, 95% CI 1.13 to 2.36; 3 studies, 745 participants) based on moderate-quality evidence.[9] No difference in tolerability between valproate and lithium was found (78% vs. 86%, OR 0.61, 95% CI 0.25 to 1.50; 2 studies, 164 participants) based on low-quality evidence.[9] Primary tolerability outcome data on the olanzapine comparison with valproate were not obtained.[9] Within the children and adolescent population, the evidence regarding any difference between valproate or placebo was uncertain (67% vs. 60%, OR 1.39, 95% CI 0.71 to 2.71; 1 study, 150 participants, very low-quality evidence).[9] Primary tolerability outcome data on the lithium or risperidone comparisons with valproate were not obtained.[9]

In summary, there is evidence that valproate is an efficacious treatment for acute mania in adults when compared to placebo.[9] By contrast, there is no evidence of a difference in efficacy between valproate and placebo for children and adolescents.[9] Valproate may be less efficacious than olanzapine in adults, and may also be inferior to risperidone as a monotherapy treatment for pediatric mania.[9]

Excluded Systematic Reviews
After review, 13 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses)[36-39], wrong study design of included trials (e.g., observational)[40-47], comparator (e.g., no control or placebo-controlled)[48,49], or outcome studied (e.g., non-clinical)[50].

NEW GUIDELINES

NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE
Epilepsy Diagnosis and Management
In February 2020 NICE strengthened guidance that valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable.[10] Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and only take valproate if they have a pregnancy prevention program in place, in line with the UK MHRA safety advice on valproate.[51] The risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child should be discussed with all women of childbearing potential.[10] NICE 2020 guidance recommends the following AEDs for each type of seizure:

Newly Diagnosed Focal Seizures
- Offer carbamazepine or lamotrigine as first-line treatment to children, young people, and adults with newly diagnosed focal seizures.[10]
- If carbamazepine or lamotrigine are unsuitable or not tolerated for newly diagnosed focal seizures: offer levetiracetam or oxcarbazepine to women and girls of childbearing potential.[10] Offer levetiracetam, oxcarbazepine or sodium valproate to boys, men and women who are not of childbearing potential.[10] If the first AED tried is ineffective, offer an alternative from these AEDs.[10]
- If first-line treatments for children, young people and adults with focal seizures are ineffective or not tolerated: offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine or topiramate as adjunctive treatment to women and girls of childbearing potential.[10] Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to boys, men and women who are not of childbearing potential.[10]

Newly Diagnosed Generalized Motor Seizures

- First-line pharmacologic treatment of newly diagnosed generalized motor seizures (GTC) is sodium valproate for boys, men and women who are not of childbearing potential.[10] Offer lamotrigine if sodium valproate is unsuitable.[10] If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures.[10] Consider carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or absence seizures.[10]
- If first-line treatments for children, young people and adults with GTC seizures are ineffective or not tolerated: offer clobazam, lamotrigine, levetiracetam or topiramate as adjunctive treatment to women and girls of childbearing potential.[10] Offer clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to boys, men and women who are not of childbearing potential.[10]

Newly Diagnosed Absence Seizures

- For first-line treatment of absence seizures offer ethosuximide to women and girls of childbearing potential.[10]
- Offer ethosuximide or sodium valproate to boys, men and women who are not of childbearing potential. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable.[10]
- Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated. [10]
- Do not offer sodium valproate to women and girls of childbearing potential unless the other options are ineffective or not tolerated and the pregnancy prevention program is in place.[10]

Cannabidiol with Clobazam for Treating Seizures Associated with Dravet Syndrome

Evidence-based recommendations for treating seizures associated with Dravet Syndrome with cannabidiol and clobazam were published by NICE December 2019.[11] Cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome in people aged 2 years and older, though, only if the frequency of convulsive seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment.[11]

Cannabidiol with Clobazam for Treating Seizures Associated with Lennox-Gastaut Syndrome

Cannabidiol with clobazam for treating seizures associated with LGS was published by NICE December 2019. Cannabidiol with clobazam is recommended as an option for treating seizures associated with LGS in people aged 2 years and older, only if the frequency of drop seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment.[12]

<u>AMERICAN ACADEMY OF NEUROLOGY AND THE AMERICAN EPILEPSY SOCIETY</u>

In 2004, the AAN and AES published guidance on use of 7 second-generation AEDs: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. Since the 2004 guideline publication, new studies emerged in the second-generation and more recently approved third-generation AEDs (eslicarbazepine, ezogabine, lacosamide, perampanel, pregabalin, and rufinamide). The FDA has since approved 2 older AEDs (clobazam and vigabatrin) for treating certain types of epileptic disorders in the United States. In 2018, The AAN and AES published guideline updates focused on the efficacy and tolerability of the more recently approved AEDs. Part 1 evaluates evidence for treatment of new-onset epilepsy with newer AEDs.[13] Part 2 evaluates evidence for treatment-resistant epilepsy with newer AEDs.[14]

For the 2018 update, the AAN and AES convened an expert panel which included adult and pediatric epileptologists, methodologic experts, pharmacists, and general neurologists. The 2004 AAN criteria[52] were used to systematically review literature through November 2015, classify pertinent studies according to the therapeutic rating scheme, and link recommendations to evidence strength.[13] The practice guidelines were developed with financial support from the AAN. Significant efforts were made to minimize the potential for conflicts of interest to influence the recommendations of these guidelines.[13] The AAN and AES separated individuals who have a financial stake in the success or failure of the products appraised in the guideline and the developers of the guidelines.[13]

Level A recommendations are considered compelling and accepted by 100% of the author panel.[52] Level B recommendations are considered convincing and accepted by more than 80% of the author panel.[52] Level C recommendations are considered plausible and accepted by more than 50% but less 80% of the author panel.[52]

Part I: Recommendations for The Use of New AEDs In New-Onset Epilepsy Include:

- Lamotrigine should (Level B) and levetiracetam and zonisamide may (Level C) be considered in decreasing seizure frequency in adults with new-onset focal epilepsy.[13]
- Lamotrigine should (Level B) and gabapentin may (Level C) be considered in decreasing seizure frequency in patients ≥60 years of age with new-onset focal epilepsy.[13]
- Unless there are compelling adverse effect–related concerns, ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (level B).[13]
- No high-quality studies suggest clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or zonisamide are effective in treating new-onset epilepsy because no high-quality studies exist in adults.[13]

Part II: Recommendations for The Use of New AEDs In Treatment-Resistant Epilepsy Include:

- The following are established as effective to reduce seizure frequency (Level A): immediate-release pregabalin and perampanel for treatment-resistant adult focal epilepsy ; vigabatrin for treatment-resistant adult focal epilepsy (not first-line treatment due to side effects); rufinamide for LGS as add-on therapy.[14]
- The following should be considered to decrease seizure frequency (Level B): lacosamide, eslicarbazepine, and extended-release topiramate for treatment-resistant adult focal epilepsy; immediate- and extended-release lamotrigine for generalized epilepsy with treatment-resistant generalized motor seizures in adults; levetiracetam (add-on therapy) for treatment-resistant childhood focal epilepsy (1 month–16 years), treatment-resistant generalized tonic-clonic seizures, and treatment-resistant juvenile myoclonic epilepsy; clobazam for LGS (add-on therapy); zonisamide for treatment-resistant childhood focal epilepsy (6–17 years); oxcarbazepine for treatment-resistant childhood focal epilepsy (1 month–4 years).[14]
- AED selection depends on seizure/syndrome type, patient age, concomitant medications, and tolerability, safety, and efficacy of AED. [14]

New Formulations or Indications:

NEW FORMULATIONS

- An oral soluble film formulation of clobazam (Sympazan™) received FDA approval in November 2018. Clobazam is indicated for adjunctive treatment of seizures associated with LGS in patients aged 2 years and older.

- Levetiracetam extended-release tablets (Elepsia XR™) received FDA approval in December 2018. Levetiracetam extended-release tablets are indicated for adjunctive therapy for the treatment of partial onset seizures in patients 12 years of age and older.

NEW FDA-APPROVED INDICATIONS

- Levetiracetam oral tablets (Keppra®) and levetiracetam extended-release oral tablets (Keppra XR®) received an expanded indication in October 2019 for the treatment of partial-onset seizures in patients 1 month of age and older. Levetiracetam was previously approved as adjunctive therapy for treatment of partial seizures in patients 1 month of age and older.

- Oxcarbazepine extended-release tablets (Oxtellar XR®) received an expanded indication as monotherapy to treat partial-onset seizures in patients 6 years and older in December 2018. Previously, oxcarbazepine was approved as adjunctive treatment for partial-onset seizures in patients 6 years and older.

- Perampanel tablets and oral suspension (Fycompa®) received expanded FDA approval in September 2018 for the treatment of partial-onset seizures with or without secondary generalized seizures in patients 4 years of age and older. Previously, perampanel was FDA-approved for use in patients 12 years of age and older.

- Brivaracetam tablets, oral solution, and intravenous injection (Briviact®) received expanded FDA approval in May 2018 for treatment of partial-onset seizures in patients 4 years of age and older. Previously, brivaracetam was approved for use in patients 16 years of age and older.

- Pregabalin capsules and oral solution (Lyrica®) received expanded FDA approval in May 2019 for adjunctive therapy in the treatment of partial-onset seizures in patients 1 month of age and older. Previously, pregabalin was approved for use in patients 4 years of age and older.

- Vigabatrin (Sabril®) received an expanded indication in January 2020 to include children 2 years of age and older with refractory complex partial seizures. Previously, vigabatrin was approved for patients 10 years age and older.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[53]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Fosphenytoin Phenytoin	Cerebyx Dilantin	7/2019	Warnings and Precautions	Fosphenytoin and phenytoin can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin (the active metabolite of Cerebryx)-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The onset of symptoms is usually within 28 days but can occur later. Fosphenytoin or phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.
Valproate Sodium, Valproic Acid, Divalproex Sodium	Depacon, Depakene, Depakote	2/2019	Boxed Warning	Fetal Risk Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following *in utero* exposure. Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.
Perampanel	Fycompa	5/2019	Warnings and Precautions	Neurologic Effects Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of perampanel is known. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when perampanel is used with other drugs with sedative properties because of potential additive effects.

Lamotrigine	Lamictal	9/2019	Warnings and Precautions	Hemophagocytic Lymphohistiocytosis Hemophagocytic lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Common findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, hypertriglyceridemia, and liver function and coagulation abnormalities. In cases of HLH reported with lamotrigine, patients have presented with signs of systemic inflammation (fever, rash, hepatosplenomegaly, and organ system dysfunction) and blood dyscrasias. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment
Gabapentin Pregabalin	Neurontin, Gralise, Horizant Lyrica Lyrica CR	12/2019	FDA Drug Safety Communication	FDA is warning that serious, life-threatening, and fatal respiratory depression has been reported with the gabapentinoids, gabapentin and pregabalin. Most cases occurred in association with co-administered central nervous system (CNS) depressants, especially opioids, in the setting of underlying respiratory impairment, or in the elderly.
Vigabatrin	Sabril	1/2020	Warnings and Precautions	Intramyelinic edema (IME) has been reported in postmortem examination of infants being treated for infantile spasms (IS) with vigabatrin.

Randomized Controlled Trials:
A total of 50 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Cenobamate (Xcopri™)
See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Cenobamate (Xcopri™) tablets are FDA-approved for treatment of partial-onset (focal) seizures in adults.[16] The recommended initial dose of oral cenobamate is 12.5 mg once daily for the first 2 weeks, followed by a slow upward titration: 25 mg once daily for weeks 3 and 4; 50 mg once daily for weeks 5 and 6; 100 mg once daily for weeks 7 and 8; 150 mg once daily for weeks 9 and 10; and 200 mg once daily (the recommended maintenance dose) for week 11 and thereafter.[16] The dose may be further increased by 50 mg once daily every two weeks if necessary based upon response and tolerability, to a maximum dose of 400 mg once daily.[16] The recommended dosage and titration schedule should not be exceeded because of the potential for serious adverse effects including drug reaction with eosinophilia and systemic symptoms (DRESS). When cenobamate is discontinued, the dose should be titrated down gradually over at least two weeks.[16]

Cenobamate is not recommended for patients with severe hepatic impairment or end-stage renal disease undergoing dialysis.[16] The maximum dose should not exceed 200 mg once daily for patients with mild to moderate hepatic impairment.[16] Lower cenobamate doses may be needed for patients with mild to moderate renal disease.[16] The drug is expected to be available in the United States in the second quarter of 2020 following scheduling review by the US Drug Enforcement Administration. Data from an unpublished phase 2 trial involving 222 patients (NCT01397968) and a published phase 2 trial in 437 patients supported the FDA approval of cenobamate.[54]

The published phase 2 study was a multicenter, double-blind, randomized, placebo-controlled, dose-response trial conducted at 107 epilepsy and neurology centers in 16 countries.[15] Adult patients with treatment-resistant focal seizures maintained on 1 to 3 AEDs were randomly assigned (1:1:1:1) to adjuvant once daily oral cenobamate 100 mg, 200 mg, 400 mg, or placebo.[15] Subjects completed an 8-week baseline assessment before starting their assigned therapy. The trial included a 6-week titration phase and 12-week maintenance phase. During the titration phase, all patients began an initial starting dose of cenobamate 100 mg per day that was up-titrated to the target dose, or a matching placebo once daily. After a blinded review of the first 9 patients, the protocol was amended to lower the starting dose of cenobamate to 50 mg per day followed by weekly dose increases of 50 mg up to the target dose. During the 6-week titration phase, if a patient did not tolerate the next higher dose, the dose could be reduced to the previous dose.[15] For the 12-week maintenance phase of the trial, cenobamate dosing was not modified. The dosing regimen used in this trial titrated cenobamate at higher and more rapid doses than the subsequent dosing recommended by the FDA. Patients continued taking their concomitant AED therapy at stabilized doses during the 18-week double blind period. The co-primary efficacy outcomes were percentage change in 28-day focal seizure frequency from baseline and responder rates (percentage of patients achieving ≥50% reduction from baseline in focal seizure frequency) over the 12-week treatment period.[15] Due to different regulatory requirements, the percentage change in focal seizure frequency was considered the primary efficacy outcome for the FDA, and the responder rate was considered the primary efficacy outcome for the European Medicines Agency (EMA).[15] The intention-to-treat (ITT) population included all randomized patients who had taken at least 1 dose of study drug and had any post-baseline seizure data.

Over 12 weeks, significant reductions in seizure frequency were observed with cenobamate compared to placebo in the ITT population. Median seizure frequency reduction from baseline was 24.0% (IQR 45.0 to 7.0%) for the placebo group compared with 35.5% (IQR 62.5 to 5.0%; p=0.0071 vs. placebo) for the 100 mg dose group, and 55.0% for the 200 mg and the 400 mg dose groups (IQR 73.0 to 23.0% and 85.0 to 28.0%, respectively, P<0.0001 vs. placebo for both doses).[15] Significantly more patients had 50% or greater reduction in seizure frequency with cenobamate versus placebo. Responder rates during the 12-week maintenance phase were 25% for the placebo group compared with 40% (OR 1.97, 95% CI 1.08 to 3.56; p=0.0365 vs. placebo) for the 100 mg dose group, 56% (OR 3.74, 95% CI 2.06 to 6.80; p<0.0001 vs. placebo) for the 200 mg dose group, and 64% (OR 5.24, 2.84 to 9.67; p<0.0001 vs. placebo) for the 400 mg dose group.[15] Moderate-quality data from this trial demonstrates adjunctive cenobamate reduced focal seizure frequency, in a dose-related fashion.[15] Adjunctive cenobamate appears to be an effective treatment option in adults with uncontrolled focal seizures when administered for 3 months at a stable maintenance dose.[15] Additional trial information is described and evaluated below in the comparative evidence summary presented in **Table 5**.

Limitations of this study include the short study duration and the potential drug interaction impact of concomitant AEDs. In addition, type of seizure and seizure frequency were self-recorded by the subjects, which could contribute to detection bias.[15] It is not clear if cenobamate is safe and effective in pediatric patients or patients with generalized seizure disorder, as these people were excluded from the phase 2 trial. Two phase 3 trials evaluating the safety and efficacy of cenobamate in patients with generalized motor seizures are currently ongoing.

Clinical Safety:

The most common AEs reported in the cenobamate trials which occurred in greater than 10% of patients were dose-dependent somnolence, dizziness, fatigue, and diplopia.[16] Discontinuation rates due to adverse effects were 11%, 9%, and 21% for patients randomized to cenobamate 100 mg, 200 mg and 400 mg once daily compared to 4% of subjects who received placebo.[16] The adverse effects that led to drug discontinuation were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo.[16] Specific adverse effect rates in the cenobamate study populations compared to placebo are presented in **Table 4**. One serious case of DRESS occurred in the 200 mg cenobamate group when cenobamate was rapidly titrated.[16] No cases of DRESS were reported when cenobamate was slowly initiated at 12.5 mg once daily and titrated up every 2 weeks to 200 mg once daily.[16] A higher percentage of subjects (31% at 200 mg) had a QT shortening of 20 msec compared to placebo (6 to 17%).[16] Familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias.[16] No deaths were reported during clinical trials with cenobamate. The FDA also notes that any patient taking an AED should be monitored for the emergence or worsening of depressive symptoms, suicidal thoughts or behaviors, or any other changes in mood.[16] There are limited data regarding the risk of cenobamate use in pregnancy or lactation, but animal data suggests possibility of fetal harm.[16] Currently, an ongoing multicenter, open-label study is being conducted to assess the safety and pharmacokinetics of cenobamate as adjunctive therapy in over 1300 subjects with partial onset seizures (NCT02535091).The cenobamate titration rate is much lower in this trial, with a starting dose of 12.5 mg and dose increases every 2 weeks.

Table 3. Adverse Reactions Associated with Cenobamate with > 5% Incidence Compared to Placebo[16]

	Cenobamate			Placebo
Adverse Reaction	**100 mg (n=108) %**	**200 mg (n=223) %**	**400 mg (n=111) %**	**n=216 %**
Vertigo	1	1	6	1
Diplopia	6	7	15	2
Nausea	6	6	9	3
Constipation	2	4	8	0
Somnolence	19	22	37	11
Dizziness	18	22	33	15
Fatigue	12	14	24	7
Headache	10	12	10	9
Balance Disorder	3	5	9	1
Gait Disturbance	1	3	8	1
Nystagmus	3	7	6	0
Ataxia	2	3	6	2

Cenobamate is extensively metabolized by hepatic enzymes. Consequently, administration of cenobamate can impact the plasma concentrations of other AEDs including lamotrigine, carbamazepine, phenytoin, phenobarbital, and clobazam. In addition, substrates of CYP2C19, CYP3A, and CYP2B6 may interact with cenobamate.

Look-alike / Sound-alike Error Risk Potential: No other medications have been identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in seizure frequency
2) Increased time of seizure freedom
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage change in seizure frequency from baseline over 3 months

Table 4. Pharmacology and Pharmacokinetic Properties.[16]

Parameter	
Mechanism of Action	Exact mechanism of action unknown: postulated that cenobamate reduces repetitive neuronal firing by inhibiting voltage-gated sodium currents; also, a modulator of the GABA receptor
Oral Bioavailability	88%
Distribution and Protein Binding	Protein Binding: 60%, Volume of Distribution: 40-50 L
Elimination	Clearance: 0.45-9.63 L/hr Excretion: Urine 87.8%; Feces 5.2%
Half-Life	50-60 hrs at doses of 100 to 400 mg once daily
Metabolism	Extensively metabolized; primarily by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5

Abbreviations: GABA= gamma-aminobutyric acid; hrs=hours; L=liter

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Krauss GL, et al.[15] MC, DB, PC, RCT, Phase 2 trial N=437	1. Cenobamate 100 mg orally once daily 2. Cenobamate 200 mg orally once daily 3. Cenobamate 400 mg orally once daily 4. Placebo orally once daily All patients continued concomitant AED regimen during the trial	Demographics: 1. Mean Age: 39 yrs 2. Male: 49% 3. Ethnicity, White: 84% 4. Taking 2-3 AEDs: 74% 5. Most frequently used concomitant AEDS: -levetiracetam: 43% -lamotrigine: 32% -carbamazepine: 30% Key Inclusion Criteria: 1. Patients aged 18 to 70 years with an ILAE diagnosis of uncontrolled focal epilepsy despite treatment with at least 1 AED within previous 2 years 2. Taking 1-3 AEDs at stable doses at least 4 weeks before screening 3. EEG reading consistent with diagnosis of focal epilepsy 4. Have at least 8 partial seizures during the 8-week baseline period Key Exclusion Criteria: 1. Patients taking diazepam, phenytoin, or phenobarbital within 1 mo of screening 2. Patients taking vigabatrin within the past 12 months, felbamate for < 18 consecutive mos, or intermittent rescue	ITT: 1. 108 2. 110 3. 111 4. 108 PP: 1. 95 2. 90 3. 81 4. 94 Attrition: 1. 13 (12%) 2. 20 (18%) 3. 30 (27%) 4. 14 (13%)	Co-Primary Endpoints: 1. Median percentage reduction from baseline in focal seizure frequency per 28 days over 12 weeks 1. 35.5% (IQR 62.5 to 15) 2. 55% (IQR 73 to 23) 3. 55% (IQR 85 to 28) 4. 24% (IQR 45 to 7) P<0.0071 for 100 mg vs. placebo p <0.0001 for 200 mg and 400 mg vs. placebo 2. 50% or more reduction in seizure frequency per 28 days over 12 weeks (responder). 1. N=41 (40%) 2. N=55 (56%) 3. N=61 (64%) 4. N=26 (25%) 1 vs. 4 OR 1.97 (95% CI 1.08 to 3.56), p<0.0365 2 vs. 4 OR 3.74 (95% CI 2.06 to 6.80), p<0.0001 3 vs. 4 OR 5.24 (95% CI 2.84 to 9.67) p<0.0001 Secondary Endpoint: 1. 75% or more reduction in seizure frequency per 28 days over 12 weeks 1. 17 (17%)	NA NA 15%/7 31%/4 39%/3	AEs 1. 70 (65%) 2. 84 (76%) 3. 100 (90%) 4. 76 (70%) SAEs 1. 10 (9%) 2. 4 (4%) 3. 8 (7%) 4. 6 (6%) AE leading to withdrawal 1. 11 (10%) 2. 15 (14%) 3. 22 (20%) 4. 5 (5%) p-values and 95% CI NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 via IWRS. Computer-generated block size of 4 within each country ensured equal allocation within each group. Baseline demographics similar between groups. Performance Bias: Low. Patients, investigators, and study personnel masked to treatment assignment. Study medication and packaging were identical in appearance to placebo. Side effects from study drug could lead to unblinding. No documentation of how potential drug-drug interactions could have impacted outcomes (seizure frequency or adverse effects). Detection Bias: Unclear. Not clear how seizure frequencies were documented and how they were assessed as they were self-reported by the subjects. Attrition Bias: High. Attrition rates varied by dose. As cenobamate dose increased, rate of AEs leading to study withdrawal increased. Reporting Bias: Unclear. Protocol not available in supplementary materials. Other Bias: Unclear. Funded by SK Life Science, Inc. Funder was responsible for study design and statistical analysis. An employee of SK Life Science is an author for the published study. The employee had a role in data analysis, data interpretation, and writing of the report. **Applicability**: Patient: Adults with focal seizures included in study. Twenty-five percent of patients were from the US. Not clear if cenobamate is safe and effective in pediatric patients or generalized seizure disorder. Intervention: Dose ranging trial, titration protocol adjusted due to patient intolerance to higher dosing.

		benzodiazepines within the past month 3. History of status epilepticus within 3 mos of screening 4. History of psychiatric illness within past 2 yrs 5. History of alcoholism or drug misuse within the past 2 yrs		2. 30 (31%) 3. 44 (46%) 4. 10 (10%) 1 vs. 4 p=0.2146 95% CI NR 2 vs. 4 p=0.0003 95% CI NR 3 vs. 4 p<0.0001 95% CI NR	 NS 21%/5 36%/3			Comparator: Placebo-controlled, cenobamate used as adjunctive therapy in subjects maintained on 1-3 AEDs. Head to head trial with another AED approved for partial seizures (e.g., eslicarbazepine, perampanel, brivaracetam, lacosamide) would be valuable. Outcomes: Seizure frequency reduction and responder rate are required by FDA and EMA respectively for drug approval. Setting: 107 epilepsy and neurology centers in 16 countries. Number of patients by country: Australia = 24 (5.5%) Bulgaria = 37 (8.5%) Czech Republic = 24 (5.5%) France = 4 (<1%) Germany = 33 (7.5%) Hungary = 15 (3.4%) Israel = 12 (2.7%) Poland = 48 (11%) Romania = 4 (<1%) Serbia = 28 (6.4%) South Korea = 31 (7%) Spain = 27 (6.2%) Thailand = 8 (1.8%) Ukraine = 23 (5.3%) UK = 8 (1.8%) USA = 111 (25%)

Abbreviations AEDs=anti-epileptic drugs; AE=adverse effects; ARR=absolute risk reduction; CI=confidence interval; EEG=electroencephalogram; EMA=European Medication Agency; FDA=Food and Drug Administration; ILAE=International League Against Epilepsy; IQR=interquartile range; ITT=intention to treat; IWRS=interactive web response system; mos=months; N=number of subjects; NA=not applicable; NR=not reported; NNH=number needed to harm; NNT=number needed to treat; PP=per protocol; SAEs=serious adverse effects; yrs=years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL	Carveout
carbamazepine	CARBAMAZEPINE	ORAL SUSP	PO	Y	
carbamazepine	TEGRETOL	ORAL SUSP	PO	Y	
carbamazepine	CARBAMAZEPINE	TAB CHEW	PO	Y	
carbamazepine	CARBAMAZEPINE ER	TAB ER 12H	PO	Y	
carbamazepine	TEGRETOL XR	TAB ER 12H	PO	Y	
carbamazepine	CARBAMAZEPINE	TABLET	PO	Y	
carbamazepine	EPITOL	TABLET	PO	Y	
carbamazepine	TEGRETOL	TABLET	PO	Y	
diazepam	DIASTAT	KIT	RC	Y	
diazepam	DIASTAT ACUDIAL	KIT	RC	Y	
diazepam	DIAZEPAM	KIT	RC	Y	
divalproex sodium	DEPAKOTE SPRINKLE	CAP DR SPR	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM	CAP DR SPR	PO	Y	Y
divalproex sodium	DEPAKOTE ER	TAB ER 24H	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM ER	TAB ER 24H	PO	Y	Y
divalproex sodium	DEPAKOTE	TABLET DR	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM	TABLET DR	PO	Y	Y
ethosuximide	ETHOSUXIMIDE	CAPSULE	PO	Y	
ethosuximide	ZARONTIN	CAPSULE	PO	Y	
ethosuximide	ETHOSUXIMIDE	SOLUTION	PO	Y	
ethosuximide	ZARONTIN	SOLUTION	PO	Y	
ethotoin	PEGANONE	TABLET	PO	Y	
gabapentin	GABAPENTIN	CAPSULE	PO	Y	
gabapentin	NEURONTIN	CAPSULE	PO	Y	
gabapentin	GABAPENTIN	TABLET	PO	Y	
gabapentin	NEURONTIN	TABLET	PO	Y	
lacosamide	VIMPAT	TABLET	PO	Y	
lamotrigine	LAMICTAL	TABLET	PO	Y	Y
lamotrigine	LAMOTRIGINE	TABLET	PO	Y	Y
lamotrigine	SUBVENITE	TABLET	PO	Y	Y
levetiracetam	KEPPRA	SOLUTION	PO	Y	
levetiracetam	LEVETIRACETAM	SOLUTION	PO	Y	
levetiracetam	KEPPRA	TABLET	PO	Y	
levetiracetam	LEVETIRACETAM	TABLET	PO	Y	
levetiracetam	ROWEEPRA	TABLET	PO	Y	
methsuximide	CELONTIN	CAPSULE	PO	Y	
oxcarbazepine	OXCARBAZEPINE	ORAL SUSP	PO	Y	
oxcarbazepine	TRILEPTAL	ORAL SUSP	PO	Y	

oxcarbazepine	OXCARBAZEPINE	TABLET	PO	Y	
oxcarbazepine	TRILEPTAL	TABLET	PO	Y	
phenobarbital	PHENOBARBITAL	ELIXIR	PO	Y	
phenobarbital	PHENOBARBITAL	TABLET	PO	Y	
phenytoin	DILANTIN-125	ORAL SUSP	PO	Y	
phenytoin	PHENYTOIN	ORAL SUSP	PO	Y	
phenytoin	DILANTIN	TAB CHEW	PO	Y	
phenytoin	PHENYTOIN	TAB CHEW	PO	Y	
phenytoin sodium extended	DILANTIN	CAPSULE	PO	Y	
phenytoin sodium extended	PHENYTEK	CAPSULE	PO	Y	
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	CAPSULE	PO	Y	
primidone	MYSOLINE	TABLET	PO	Y	
primidone	PRIMIDONE	TABLET	PO	Y	
rufinamide	BANZEL	TABLET	PO	Y	
tiagabine HCl	GABITRIL	TABLET	PO	Y	
tiagabine HCl	TIAGABINE HCL	TABLET	PO	Y	
topiramate	TOPAMAX	TABLET	PO	Y	
topiramate	TOPIRAMATE	TABLET	PO	Y	
valproic acid	VALPROIC ACID	CAPSULE	PO	Y	Y
valproic acid (as sodium salt)	VALPROIC ACID	SOLUTION	PO	Y	Y
zonisamide	ZONISAMIDE	CAPSULE	PO	Y	
lamotrigine	LAMICTAL (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL XR	TAB ER 24	PO	V	Y
lamotrigine	LAMOTRIGINE ER	TAB ER 24	PO	V	Y
lamotrigine	LAMICTAL ODT	TAB RAPDIS	PO	V	Y
lamotrigine	LAMOTRIGINE ODT	TAB RAPDIS	PO	V	Y
lamotrigine	LAMICTAL	TB CHW DSP	PO	V	Y
lamotrigine	LAMOTRIGINE	TB CHW DSP	PO	V	Y
lamotrigine	LAMICTAL XR (BLUE)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL XR (GREEN)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL XR (ORANGE)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL ODT (BLUE)	TB RD DSPK	PO	V	Y

lamotrigine	LAMICTAL ODT (GREEN)	TB RD DSPK	PO	V	Y
lamotrigine	LAMICTAL ODT (ORANGE)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (BLUE)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (GREEN)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (ORANGE)	TB RD DSPK	PO	V	Y
brivaracetam	BRIVIACT	SOLUTION	PO	N	
brivaracetam	BRIVIACT	TABLET	PO	N	
cannabidiol (CBD)	EPIDIOLEX	SOLUTION	PO	N	
carbamazepine	CARBAMAZEPINE ER	CPMP 12HR	PO	N	
carbamazepine	CARBATROL	CPMP 12HR	PO	N	
clobazam	SYMPAZAN	FILM	PO	N	
clobazam	CLOBAZAM	ORAL SUSP	PO	N	
clobazam	ONFI	ORAL SUSP	PO	N	
clobazam	CLOBAZAM	TABLET	PO	N	
clobazam	ONFI	TABLET	PO	N	
eslicarbazepine acetate	APTIOM	TABLET	PO	N	
felbamate	FELBAMATE	ORAL SUSP	PO	N	
felbamate	FELBATOL	ORAL SUSP	PO	N	
felbamate	FELBAMATE	TABLET	PO	N	
felbamate	FELBATOL	TABLET	PO	N	
gabapentin	GABAPENTIN	SOLUTION	PO	N	
gabapentin	NEURONTIN	SOLUTION	PO	N	
gabapentin	GRALISE	TAB ER 24H	PO	N	
gabapentin enacarbil	HORIZANT	TABLET ER	PO	N	
gabapentin/lidocaine	GABACAINE	KIT	MC	N	
lacosamide	VIMPAT	SOLUTION	PO	N	
lacosamide	VIMPAT	TAB DS PK	PO	N	
levetiracetam	KEPPRA XR	TAB ER 24H	PO	N	
levetiracetam	LEVETIRACETAM ER	TAB ER 24H	PO	N	
levetiracetam	ROWEEPRA XR	TAB ER 24H	PO	N	
levetiracetam	SPRITAM	TAB SUSP	PO	N	
midazolam	NAYZILAM	SPRAY	NS	N	
oxcarbazepine	OXTELLAR XR	TAB ER 24H	PO	N	
perampanel	FYCOMPA	ORAL SUSP	PO	N	
perampanel	FYCOMPA	TAB DS PK	PO	N	
perampanel	FYCOMPA	TABLET	PO	N	
pregabalin	LYRICA	CAPSULE	PO	N	
pregabalin	PREGABALIN	CAPSULE	PO	N	
pregabalin	LYRICA	SOLUTION	PO	N	
pregabalin	PREGABALIN	SOLUTION	PO	N	

rufinamide	BANZEL	ORAL SUSP	PO	N	
stiripentol	DIACOMIT	CAPSULE	PO	N	
stiripentol	DIACOMIT	POWD PACK	PO	N	
topiramate	TROKENDI XR	CAP ER 24H	PO	N	
topiramate	QUDEXY XR	CAP SPR 24	PO	N	
topiramate	TOPIRAMATE ER	CAP SPR 24	PO	N	
topiramate	TOPAMAX	CAP SPRINK	PO	N	
topiramate	TOPIRAMATE	CAP SPRINK	PO	N	
vigabatrin	SABRIL	POWD PACK	PO	N	
vigabatrin	VIGABATRIN	POWD PACK	PO	N	
vigabatrin	VIGADRONE	POWD PACK	PO	N	
vigabatrin	SABRIL	TABLET	PO	N	
vigabatrin	VIGABATRIN	TABLET	PO	N	
carbamazepine	EQUETRO	CPMP 12HR	PO		Y
phenobarbital	PHENOBARBITAL	ELIXIR	PO		

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 5 2020, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 11, 2020

1	Carbamazepine	4733
2	Diazepam/	3225
3	divalproex.mp. or Valproic Acid/	6988
4	Ethosuximide/	224
5	ethotoin.mp.	2
6	lacosamide.mp.	772
7	lamotrigine.mp.	4081
8	levetiracetam.mp.	3355
9	methsuximide.mp.	12
10	oxcarbazepine.mp.	1501
11	Phenobarbital/	2109
12	Phenytoin/	2372
14	Primidone/	106
14	rufinamide.mp.	240
15	tiagabine.mp.	594
16	topiramate.mp.	3849
17	Valproic Acid/	6759
18	zonisamide.mp.	997
19	brivaracetam.mp.	231
20	clobazam.mp.	534
21	esclicarbazepine.mp.	2
22	felbamate.mp.	325
23	perampanel.mp.	434
24	Pregabalin/	1714
25	Vigabatrin/	663
26	Gabapentin	2655
27	midazolam spray.mp	9
28	stiripentol.mp	177
29	Cannabidiol/	1077
30	cenobamate.mp	7
31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30:	33279
32	Epilepsy/	33169
33	31 and 32	4602
34	limit 29 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	50

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XCOPRI safely and effectively. See full prescribing information for XCOPRI.

XCOPRI® (cenobamate tablets), for oral use, [controlled substance schedule pending]
Initial U.S. Approval: XXXX [pending controlled substance scheduling]

INDICATIONS AND USAGE

XCOPRI is indicated for the treatment of partial-onset seizures in adult patients. (1)

DOSAGE AND ADMINISTRATION

- Swallow tablets whole. Do not crush or chew. (2.1)
- The recommended initial dosage of XCOPRI is 12.5 mg once daily, titrated to the recommended maintenance dosage of 200 mg once daily. The recommended titration schedule should not be exceeded. The maximum dosage is 400 mg once daily. (2.2)
- Hepatic impairment: For patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200 mg once daily. (2.3, 8.7, 12.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. (3)

CONTRAINDICATIONS

- Hypersensitivity to cenobamate or any of the inactive ingredients in XCOPRI. (4)
- Familial Short QT syndrome. (4)

WARNINGS AND PRECAUTIONS

- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity:* Discontinue if no alternate etiology. (5.1)
- *QT Shortening:* Use caution when administering XCOPRI with other drugs that shorten the QT interval (5.2)
- *Suicidal Behavior and Ideation*: Monitor patients for suicidal behavior and ideation. (5.3)
- *Neurological Adverse Reactions*: Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on XCOPRI. Concomitant use with other CNS depressants or alcohol may have additive effects. (5.4)
- *Withdrawal of Antiepileptic Drugs*: XCOPRI should be gradually withdrawn to minimize the potential of increased seizure frequency. (5.5)

ADVERSE REACTIONS

The most common adverse reactions in patients receiving XCOPRI (at least 10% for XCOPRI and more frequently than placebo) include somnolence, dizziness, fatigue, diplopia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SK Life Science, Inc. at 1-866-657-5574 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Phenytoin: Gradually decrease phenytoin dosage by up to 50% (7.1)
- Phenobarbital and Clobazam: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Lamotrigine, Carbamazepine: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2B6 and CYP3A Substrates: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2C19 Substrates: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Oral Contraceptives: Effectiveness of hormonal oral contraceptives may be reduced when administered concomitantly with XCOPRI. Women should use additional or alternative non-hormonal birth control. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Renal Impairment: Use with caution and dosage reduction may be considered in patients with mild to moderate (CLcr 30 to < 90 mL/min) and severe (CLcr < 30 mL/min) renal impairment. Use not recommended in end-stage renal disease (CLcr < 15 mL/min) undergoing dialysis. (8.6)
- Hepatic Impairment: Use with caution in patients with mild to moderate hepatic impairment; lower maximum dosage and additional dosage reduction may be considered. Use of XCOPRI in patients with severe hepatic impairment is not recommended. (2.3, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication? (Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older).	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication? AND Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the prescribed dose greater than 20mg/kg/day?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No**: Go to # 6
6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records? AND If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny for lack of treatment response.
3. Is the prescribed dose greater than 20mg/kg/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 4
4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. June 2018.

P&T/DUR Review: 6/2020 (DM); 3/19; 1/19 (DM)
Implementation: 5/1/19; 3/1/19

Clobazam

Goal(s): To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:
- 12 months

Requires PA:
Clobazam

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	**Yes:** Go to #3	**No:** Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.[1]

1.National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: *6/2020 (DM); 1/19 (DM); 3/18; 7/16; 3/15; 5/12*
Implementation: *3/1/19; 8/16, 8/12*

Pregabalin

Goal(s):

- Provide coverage only for funded Oregon Health Plan diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for pregabalin immediate release?	**Yes:** Go to # 3	No: Go to #4
3. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to # 4
4. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Approve for 90 days, with subsequent approvals dependent on documented positive response for lifetime approval.	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Non-funded		
Fibromyalgia	X	

Implementation: *10/18, 4/18/15; 1/11; 1/10*

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

Length of Authorization:

- Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 2 years of age and older taking clobazam?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Are baseline white blood cell (WBC) and platelet counts on file within the past 3 months? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Go to # 2 Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 6/2020 (DM); 1/19 (DM)
Implementation: 3/1/2019

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime.	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.

Approval Criteria		
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *6/2020 (DM); 5/19 (KS); 1/19 (DM); 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*