Xcopri (cenobamate)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations, or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Xcopri (cenobamate) policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Xcopri is indicated for the treatment of partial-onset seizures in adult patients.

POLICY

Criteria for Initial Approval

A. Xcopri (cenobamate) may be considered **medically necessary** for the treatment of partial-onset seizures in adults when ALL the following criteria is met:
   1. The member is 18 years of age or older
   2. The member has a diagnosis of partial-onset seizures
   3. The requested medication is prescribed by, or in consultation with, a neurologist
   4. The member has had a trial of at least TWO antiepileptic medications and experienced an inadequate treatment response, intolerance, FDA labeled contraindication, or hypersensitivity to the alternative antiepileptic medications, OR the member is currently receiving a positive therapeutic outcome on the requested medication through health insurance (excludes obtainment as samples or via manufacturer’s patient assistance programs) and experiencing a positive therapeutic outcome.

      Examples of antiepileptic drugs: carbamazepine, divalproex, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, valproic acid, zonisamide

5. The member does NOT have familial short QT syndrome

Approval will be for **12 months.**

Continuation of Therapy

A. Xcopri (cenobamate) may be considered **medically necessary** for the continuation of treatment of partial-onset seizures in adults when ALL the following criteria is met:
   1. The requested medication is prescribed by, or in consultation with, a neurologist
   2. The member has experienced a positive clinical response to therapy as defined by a decrease in seizure frequency or maintained reduction in seizures

Approval will be for **12 months.**

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

Titration blister packs – 1 pack per 28 days (at initiation of therapy)
Maintenance blister packs – 1 pack per 28 days
Xcopri 50 mg tablet – 30 tablets per 30 days
Xcopri 100 mg tablet – 30 tablets per 30 days
Xcopri 150 mg tablet – 60 tablets per 30 days
Xcopri 200 mg tablet – 60 tablets per 30 days

CLINICAL RATIONALE

Epilepsy is a disease of the brain defined by any one of the following: two or more unprovoked or reflex seizures occurring more than 24 hours apart, single unprovoked (or reflex) seizure and greater than a 60% risk of recurrence over the next 10 years, or a diagnosis of an epilepsy syndrome. More than 70 million people worldwide are affected by epilepsy. In the United States, the estimated prevalence of epilepsy of all causes is 8.5 cases per 1,000 people, or just less than 1% of the population. Uncontrolled epilepsy is associated with medical comorbidities as well as Sudden Unexpected Death in Epilepsy (SUDEP), defined as death in a person with epilepsy without any other cause. It is also associated with depression, anxiety, psychosis, and an increased risk of suicidal ideation, with suicide prevalence double that of the general population. The goal of treatment is for patients with epilepsy to become seizure free. However, seizure freedom with initial AED monotherapy is achieved in only 47% of patients. Nearly 30% of patients require multiple AEDs for treatment, increasing the risk of adverse effects and drug interactions.

Epilepsy can be diagnosed based on history, physical and neurological examination, laboratory testing as indicated, and electroencephalography (EEG) and neuroimaging findings. Seizures are first categorized into focal or generalized onset or unknown onset seizures. Seizure classifications were updated in 2017, with the term “partial” changed to “focal”, with further subdivision based on awareness (aware vs. impaired awareness). Retained awareness means the person is aware of self and environment during the seizure, even if immobile. A focal aware seizure corresponds to the prior term simple partial seizure. Impaired awareness during any part of the seizure renders it a focal impaired awareness seizure, which corresponds to the prior term of complex partial seizure. Focal-onset seizures originate within networks of one hemisphere, whereas generalized seizures engage bilateral networks from onset. A seizure should be classified as having a focal or generalized onset only if there is a ≥ 80% degree of confidence in the accuracy of determination; otherwise, the seizure should remain unclassified until more information is

available. Seizure classification is important in selecting initial AED therapy, as certain AEDs may be helpful or harmful depending on seizure type.

The 2018 American Academy of Neurology (AAN) practice guidelines recommend Lamictal (lamotrigine), Keppra (levetiracetam), and Zonegran (zonisamide) for the treatment of new-onset focal epilepsy; with Lamictal (lamotrigine) and Neurontin (gabapentin) recommended for patients ≥ 60 years of age. The 2017 American Family Physician (AFP) key practice recommendations for the initial treatment of focal seizures include the use of Tegretol (carbamazepine), Keppra (levetiracetam), Dilantin (phenytoin), and Zonegran (zonisamide) for adults 16 years to 59 years of age and Neurontin (gabapentin) and Lamictal (lamotrigine) for adults aged 60 years and older. Monotherapy with all indicated AEDs is recommended prior to use of combination AED therapy. For treatment-resistant focal epilepsy, AAN recommends Lyrica (pregabalin) and Fycompa (perampanel); Vimpat (lacosamide), Aptiom (eslicarbazepine), and Trokendi XR (topiramate ER) may also be considered for use.

Efficacy

The efficacy of Xcopri for the treatment of partial-onset seizures was established in two multicenter, randomized, double-blind, placebo-controlled studies in adult patients (Study 1 and Study 2). Patients enrolled in the studies had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have at least 3 or 4 partial-onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks. In these studies, patients had a mean duration of epilepsy of approximately 24 years and median baseline seizure frequency of 8.5 seizures per 28 days. More than 80% of patients were taking 2 or more concomitant AEDs.

Study 1 compared doses of Xcopri 200 mg/day with placebo. Study 2 compared doses of Xcopri 100 mg/day, 200 mg/day, and 400 mg/day with placebo. Both studies had an 8-week baseline period to establish a baseline seizure frequency, following which patients were randomized to a treatment arm. Patients entered a treatment period consisting of an initial titration phase (6 weeks), and a subsequent maintenance phase (6 weeks for Study 1 and 12 weeks for Study 2). In Study 1, patients were started on a daily dose of 50 mg (a higher starting dose than currently recommended) and subsequently increased by 50 mg/day every two weeks, until the final daily target dose of 200 mg/day was achieved. In Study 2, patients were started on a daily dose of 50 mg (a higher starting dose than currently recommended) and subsequently increased by 50 mg/day every week (a faster titration than currently recommended) until 100 mg/day or 200 mg/day was reached and then increased by 100 mg/day every week in patients randomized to 400 mg/day.

The primary efficacy outcome in Study 1 and Study 2 was the percent change from baseline in seizure frequency per 28 days in the treatment period. Results showed superiority of Xcopri to placebo at all doses with a dose-dependent effect. Xcopri decreased seizure frequency in adult patients with focal seizures who were not adequately treated with 1 to 3 AEDs.

Safety

The most common adverse reactions, occurring in at least 10% of patients, included somnolence, dizziness, fatigue, diplopia, and headache. Xcopri has been associated with DRESS, also known as multiorgan hypersensitivity, when titrated rapidly. Xcopri is contraindicated in patients with familial short QT syndrome as it was shown in clinical trials to shorten the QT interval by a higher percentage compared to placebo. Caution should be used when administering Xcopri with other drugs that shorten the QT interval, as there may be a synergistic effect. Xcopri is a schedule V controlled substance.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- N/A

REFERENCES

- Xcopri [package insert]. Paramus, NJ: SK Life Science, Inc.; April 2021.
- Kanner AM, Ashman E, Gloss D et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018a; 91(2):74-81.
- Kanner AM, Ashman E, Gloss D et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018b; 91(2):82-90.
- Krauss G, Klein P, Brandt C et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *Lancet Neurol*. 2020; 19:38-48.
- LaPenna P, Tormoehlen LM. The pharmacology and toxicology of third-generation anticonvulsant drugs. *J Med Toxicol.* 2017; 13(4):329-342.
- Liu G, Slater N, Perkins A. Epilepsy: treatment options. *Am Fam Physician.* 2017; 96(2):87-96.
- National Institute of Health and Care Excellence (NICE). Epilepsies: diagnosis and management. Published 2020 February. URL: https://www.nice.org.uk/guidance/cg137. Available from Internet. Accessed 2020 February 24.
- Food and Drug Administration (FDA). FDA Xcopri clinical review document. 2019 November. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212839Orig1s000MedR.pdf. Available from Internet. Accessed 2020 February 24.
- Zaccara G, Giovannelli F, Giorgi FS et al. Tolerability of new antiepileptic drugs: a network meta-analysis. *Eur J Clin Pharmacol*. 2017; 73(7):811-817.

POLICY HISTORY

Policy #: 05.04.12
Original Effective Date: September 14, 2020
Reviewed: July 2022
Revised: July 2021
Current Effective Date: August 30, 2021