PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Clobazam Products Prior Authorization Policy
- Onfi® (clobazam tablets and oral suspension – Lundbeck, generics)
- Sympazan™ (clobazam oral soluble film – Aquestive Therapeutics)

REVIEW DATE: 11/18/2020

OVERVIEW

All forms of clobazam are indicated for the adjunctive treatment of seizures associated with **Lennox-Gastaut syndrome** (LGS) in patients ≥ 2 years of age.[1,2]

Clobazam is a benzodiazepine.[1,2] The exact mechanism of action is not fully understood but is thought to involve potentiation of gamma-aminobutyric acid (GABA)ergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

Disease Overview

Lennox-Gastaut syndrome (LGS), a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[3,4] LGS most often begins between 3 and 5 years of age and comprises approximately 4% to 10% of childhood epilepsies; the prevalence is 0.26 per 1,000 people.[3-6] Children may develop normally before onset of seizures and then lose previously acquired skills (psychomotor regression), and because the seizures associated with LGS are usually resistant to treatment, intellectual impairment and learning problems may worsen over time.[6] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness, also called drop seizures) and tonic seizures (increased muscle tone and muscle stiffness).[3,6] The three main forms of treatment of LGS are antiepileptic drugs (AEDs), dietary therapy (typically the ketogenic diet), and device/surgery (e.g., Vagus nerve stimulation, corpus callosotomy).[6] None of the therapies are effective in all cases of LGS and the disorder has proven particularly resistant to most therapeutic options. The choice of treatment should take into consideration the patient's age and other associated conditions.

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[7,8] It's been estimated that 1 out of 15,700 infants born in the US are affected with Dravet syndrome. The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[8] As the seizures continue, most of the children develop some level of developmental disability and other conditions associated with the syndrome. Two or more AEDs are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[9,10] Some patients respond to the ketogenic diet and/or vagus nerve stimulation.

Guidelines/Recommendations

Lennox-Gastaut Syndrome

Currently, the FDA-approved drugs for this condition are Epidiolex® (cannabidiol oral solution), felbamate, lamotrigine, Banzel® (rufinamide tablet, oral suspension), topiramate, and clobazam.[11] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[5,6,12] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[4] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If

seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There are limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two AEDs should be used concomitantly; use of multiple AEDs raise the risk of side effects and/or drug-drug interactions.

Dravet Syndrome

Valproic acid and clobazam are considered to be the first-line treatment for Dravet syndrome.[7,9,10] If seizure control is suboptimal, Diacomit® (stiripentol capsules), Epidiolex® (cannabidiol oral solution), Fintepla® (fenfluramine oral solution), and topiramate are treatment options. Ketogenic diet is moderately effective and can also be considered second-line. If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide. Drugs that should be avoided in Dravet syndrome include sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin), Sabril® (vigabatrin tablet, oral packet), and tiagabine.

The American Academy of Neurology (AAN) and the American Epilepsy Society published a guideline update for treatment-resistant epilepsy (2018) stating that clobazam is probably effective as add-on therapy for LGS and is possibly effective as add-on therapy for treatment-resistant adult focal epilepsy.[13] Adjunctive therapy with clobazam has been effective in the treatment of uncontrolled or refractory epilepsy in adults and children.[14] If first-line treatment is ineffective or not tolerated, clobazam has been used as adjunctive treatment of refractory focal seizures (partial seizure and localization-related seizure) in children, young adults, and adults; adjunctive treatment of generalized tonic-clonic seizures in children, young adults, and adults; and adjunctive treatment of children and young adults with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of clobazam. Because of the specialized skills required for evaluation and diagnosis of patients treated with clobazam as well as the monitoring required for adverse events and long-term efficacy, initial approval requires clobazam to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of clobazam is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Lennox-Gastaut Syndrome.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs (e.g., valproic acid, levetiracetam, zonisamide, perampanel, vigabatrin, others) OR one of lamotrigine, topiramate, rufinamide, felbamate, or Epidiolex; AND
     - **iii.** Clobazam is prescribed by, or in consultation with, a neurologist.
   - **B)** Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.

Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

Other Uses with Supportive Evidence

2. **Dravet Syndrome.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i and ii)
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Clobazam is prescribed by, or in consultation with, a neurologist.
   - **B)** Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.
     Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

3. **Treatment-Refractory Seizures/Epilepsy.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
       Note: Examples are valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate.
     - **iii.** Clobazam is prescribed by, or in consultation with, a neurologist.
   - **B)** Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.
     Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of clobazam is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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4. Cross JH, Auvin S, Falip M, et al. Expert opinion on the management of Lennox-Gastaut syndrome: treatment algorithms and practical considerations. *Front Neurol*. 2017;8:505.
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13. 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. 2018;91:82-90.
14. IBM Micromedex®. IBM Corporation 2020. Available at: https://www.micromedexsolutions.com/. Accessed on November 16, 2020. Search terms: clobazam.