**BANZEL (RUFINAMIDE), ONFI (CLOBAZAM) AND SYMPAZAN (CLOBAZAM)**

**DESCRIPTION**

The intent of the Sympazan® (clobazam), Onfi® (clobazam) and Banzel® (rufinamide) policy is to ensure appropriate selection of patients for Sympazan, Onfi or Banzel use based on product labeling and/or clinical guidelines and/or clinical studies. The U.S. Food and Drug Administration (FDA) has approved Sympazan, Banzel and Onfi for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). Compendial uses include Dravet syndrome and treatment-resistant adult focal epilepsy. A North American Consensus Panel recommends the use of clobazam as a first-line treatment option for Dravet Syndrome. In addition, the American Academy of Neurology and the American Epilepsy Society consider Banzel to be an effective second-line option for adjunctive treatment of treatment-resistant adult focal epilepsy. Banzel, a triazole derivative that modulates the activity of sodium channels and subsequently prolongs the inactive state of the channel, is indicated for use in patients 1 year of age and older. It is contraindicated in patients with Familial Short QT Syndrome. Onfi and Sympazan, are a benzodiazepine, indicated for use in patients 2 years of age and older.

**POLICY**

**Initial Criteria for Approval**

I. **BANZEL** may be considered **medically necessary** for the treatment of Lennox-Gastaut Syndrome when all of the following criteria are met:
   a) Diagnosis of Lennox-Gastaut Syndrome
   b) At least one year of age
   c) Patient is taking another antiepileptic drug (AED) for the treatment of Lennox-Gastaut Syndrome

   **Approval** will be for **36 months**.

II. **BANZEL** may be considered **medically necessary** for the treatment of treatment-resistant adult focal epilepsy when all of the following criteria are met:
   a) Diagnosis of focal seizures
   b) At least 18 years of age
   c) Patient is taking another antiepileptic drug (AED) for the treatment of focal seizures
   d) Patient has failed first-line therapy prior to request for Banzel
• Failure is defined as an inability to achieve sustained seizure freedom despite adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination)

**Approval** will be for 36 months.

III. Onfi may be considered **medically necessary** for the treatment of Lennox-Gastaut when all of the following criteria are met:
   a) Diagnosis of Lennox-Gastaut Syndrome
   b) At least 2 years of age
   c) Patient is taking another antiepileptic drug (AED) for the treatment of Lennox-Gastaut Syndrome

**Approval** will be for 36 months.

IV. Onfi may be considered medically necessary for the treatment of Dravet syndrome when all of the following criteria are met:
   a) Diagnosis of Dravet syndrome
   b) At least 2 years of age

**Approval** will be for 36 months.

V. Sympazan may be considered **medically necessary** for the treatment of Lennox-Gastaut when all of the following criteria are met:
   a) Diagnosis of Lennox-Gastaut Syndrome
   b) At least 2 years of age
   c) Patient is taking another antiepileptic drug (AED) for the treatment of Lennox-Gastaut Syndrome
   d) Patient is unable to take both clobazam tablets and oral suspension due to an allergy, intolerance, or contraindication to the excipients

**Approval** will be for 36 months.

VI. Sympazan may be considered medically necessary for the treatment of Dravet syndrome when all of the following criteria are met:
   a) Diagnosis of Dravet syndrome
   b) At least 2 years of age
   c) Patient is unable to take both clobazam tablets and oral suspension due to an allergy, intolerance, or contraindication to the excipients

**Approval** will be for 36 months.

d) Banzel and Onfi are considered **not medically necessary** for patients who do not meet the criteria set forth above.

**Continuation of Therapy**
All patients (including new patients) requesting authorization for continuation of therapy must meet initial authorization criteria.
Quantity limits apply:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Generic Name</th>
<th>Strength</th>
<th>Drug Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banzel</td>
<td>rufinamide</td>
<td>200 mg, 400 mg</td>
<td>tablet</td>
<td>240 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg/mL</td>
<td>suspension</td>
<td>2400 mL/30 days</td>
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<tr>
<td>Onfi</td>
<td>clobazam</td>
<td>10 mg</td>
<td>tablet</td>
<td>120 tablets/30 days</td>
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<tr>
<td></td>
<td></td>
<td>20 mg</td>
<td>tablet</td>
<td>60 tablets/30 days</td>
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<td></td>
<td></td>
<td>2.5mg/mL</td>
<td>suspension</td>
<td>480 mL/30 days</td>
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<td>Sympazan</td>
<td>clobazam</td>
<td>5 mg</td>
<td>oral film</td>
<td>1 box or 60 films/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>oral film</td>
<td>1 box or 60 films/30 days</td>
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<td></td>
<td></td>
<td>20 mg</td>
<td>oral film</td>
<td>1 box or 60 films/30 days</td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**

Lennox-Gastaut syndrome (LGS) is a rare and debilitating form of childhood-onset epilepsy characterized by frequent seizures and multiple seizure types. Most children with LGS experience some degree of impaired intellectual functioning or information processing, along with developmental delays and behavioral disturbances. LGS seizures are often treatment-resistant, with many patients receiving multiple antiepileptic drugs (AEDs).

Treatment-resistant adult focal epilepsy is localized to one hemisphere of the brain in which awareness may be retained or impaired during the seizure. Also referred to as partial seizures, focal seizures represent 75% of treatment-resistant epilepsies.

**Efficacy**

**Banzel**

The efficacy of Banzel was established in a single, randomized, double-blind, placebo-controlled trial. This 12 week study included 138 patients between 4 and 30 years of age with a diagnosis of inadequately controlled seizures associated with LGS who were being treated with 1 to 3 concomitant stable dose AEDs. After completing a 4 week baseline phase on stable AED therapy, patients were randomized to receive either Banzel (target dose of 45mg/kg/day, maximum of 3200mg/day) or placebo as add-on therapy to their current AED regimen.

Banzel adjunctive therapy was significantly better than placebo in reducing both total seizure frequency per 28 days and tonic-atonic seizure frequency per 28 days. Banzel add-on therapy was also associated with a significantly greater improvement in seizure severity as compared to placebo.

On February 12, 2015, Banzel was approved to be used in pediatric patients ages 1 year and older for the treatment of seizures associated with Lennox-Gastaut Syndrome based on a single multi-center, open label, active-controlled randomized pharmacokinetic bridging study. The pharmacokinetic profile of Banzel is not significantly affected by age either as a continuous covariate (one to 35 years) or as a categorical covariate (age categories: 1 to less than 4 years and 4 years of age and older), after body weight is taken into consideration.

Three different randomized, double-blind, placebo-controlled trials have assessed the efficacy of Banzel for the treatment of inadequately controlled partial seizures. Study populations ranged from 313-647 participants. All three studies included adolescents and adults. Participants were receiving stable doses...
of 1-3 antiepileptic drugs at baseline and for the duration of the studies. Primary outcomes assessed included percent change in partial seizure frequency relative to baseline and seizure frequency during the study period. An intention-to-treat analysis was performed in each study.

Statistical significance was achieved in all three studies at doses of 400 mg/day or above. In one study, the percent change in seizure frequency from baseline was a decrease of 20.4% for the treatment group and an increase of 1.6% in the placebo group. In another study, there was at least a 50% reduction in seizure frequency for 32.5% of the treatment participants, compared to 14.3% of those receiving placebo. The third study found a dose-dependent decrease in frequency, favoring rufinamide over placebo.

**Onfi**
The efficacy of Onfi as adjunctive therapy for drop seizures associated with LGS was evaluated in two randomized, double-blind controlled studies and one open-label extension (OLE) study. Both randomized, double-blind studies were multicenter trials with similar patient populations in regards to disease characteristics and concomitant antiepileptic drug AED use. In these trials, patients were stratified by weight and then randomly assigned to one of 4 treatment arms: placebo, low-dosage Onfi (target dose of 0.25mg/kg/day, maximum dose of 10mg/day), medium-dosage Onfi (target dose of 0.50mg/kg/day, maximum dose of 20mg/day) or high-dosage Onfi (target dose of 1 mg/kg/day, maximum dose of 40mg/day).

Onfi significantly reduced weekly drop seizure rates in both studies, with the observed benefit of Onfi becoming greater as the dose was increased ($p < 0.0001$).

**Sympazan**
The efficacy of Sympazan as adjunctive therapy for drop seizures associated with LGS was evaluated in two randomized, double-blind studies. The first study stratified patients by weight and then randomized to treatment with three target maintenance doses (5, 10, or 20 mg daily) of clobazam or placebo. All three doses were found to significantly reduce weekly drop seizure rate compared to placebo, with a dose dependent effect observed.

The second study was a comparison study, with patients stratified by weight and randomized to either low or high dose clobazam. The reduction in seizure frequency was significantly greater in the high-dose group compared to the low-dose group.

**Safety**

**Banzel**
In all patients treated with Banzel in double-blind, adjunctive therapy studies, the most frequently observed adverse reactions ($\geq 10\%$ and greater than placebo) were headache, dizziness, somnolence, fatigue, vomiting and nausea. The adverse events most frequently responsible for study withdrawal were convulsions, nausea, vomiting, fatigue, headache, dizziness, ataxia and rash.

QT interval shortening has been demonstrated with Banzel use. Although the degree of QT interval shortening is without any known clinical risk, due to their increased risk of sudden death and ventricular arrhythmias, patients with Familial Short QT Syndrome should not take Banzel.

**Onfi and Sympazan**
The most frequent side-effects of Onfi are drowsiness, sedation and hangover effects; these central nervous system (CNS) depressive effects have occurred in up to 50% of patients treated with Onfi. Other common adverse effects associated with Onfi use include pyrexia, salivary hypersecretion, constipation, aggression, hypomania and mania. The adverse events most frequently responsible for treatment discontinuation were lethargy, somnolence, ataxia, aggression, fatigue and insomnia.
The most frequently reported side effects associated with discontinuation of treatment in clinical trials were lethargy, somnolence, ataxia, aggression, fatigue, and insomnia.

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with Onfi and Sympazan in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. Onfi should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Onfi and Sympazan have been classified as a Schedule IV controlled substance. As such, patients with a history of substance abuse should be monitored closely for signs and symptoms of habituation and dependence during therapy.

**PROCEDURES AND BILLING CODES**

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

- Code(s), if applicable.

**REFERENCES**


### POLICY HISTORY

**Policy #:** 05.01.55  
**Policy Creation:** February 2012  
**Reviewed:** July 2018  
**Revised:** January 2019  
**Current Effective Date:** March 8, 2019