### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Firdapse</strong>® (amifampridine) oral tablet</td>
<td>● Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults</td>
<td><strong>LEMS:</strong></td>
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<tr>
<td></td>
<td></td>
<td>- The recommended starting dosage is 15 mg to 30 mg daily, taken orally in divided doses (3 to 4 times daily)</td>
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<td></td>
<td></td>
<td>- The dosage can be increased by 5 mg daily every 3 to 4 days</td>
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<td></td>
<td></td>
<td>- The maximum single dose is 20 mg and the maximum total daily dosage is 80 mg</td>
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<tr>
<td><strong>Ruzurgi</strong>® (amifampridine) oral tablet</td>
<td>● Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age</td>
<td><strong>Pediatric patients 6 to less than 17 years of age weighing 45 kg or more:</strong></td>
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<tr>
<td></td>
<td></td>
<td>- Initial dosage 15 mg to 30 mg daily, in divided doses (2 to 3 times per day)</td>
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<tr>
<td></td>
<td></td>
<td>- Increase daily in 5 mg to 10 mg increments, divided in up to 5 doses per day</td>
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<tr>
<td></td>
<td></td>
<td>- The maximum single dose is 30 mg and the maximum total daily maintenance dose is 100 mg</td>
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<tr>
<td></td>
<td></td>
<td><strong>Pediatric patients 6 to less than 17 years of age weighing less than 45 kg:</strong></td>
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</tbody>
</table>

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, FocusRx, KeyRx and Health Insurance Marketplace formularies.

This is a FlexRx standard and GenRx standard prior authorization.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.
CLINICAL RATIONALE
Lambert-Eaton myasthenic syndrome
Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by the gradual onset of muscle weakness, especially of the pelvic and thigh muscles. Approximately 60 percent of LEMS cases are associated with a small cell lung cancer (SCLC), and the onset of LEMS symptoms often precedes the detection of the cancer. The LEMS patients with cancer tend to be older and nearly always have a long history of smoking. In cases in which there is no associated cancer, disease onset can be at any age.2

LEMS is characterized by weakness and fatigue especially of the pelvic and thigh muscles. The disease may affect the patient’s ability to engage in strenuous exercise and may make such activities as climbing stairs or walking up a steep walkway difficult. Onset is gradual, typically taking place over several weeks to many months. There is often a progression of symptoms whereby the shoulder muscles, muscles of the feet & hands, speech & swallowing muscles and eye muscles are affected in a stepwise fashion. The symptoms progress more quickly when LEMS is associated with cancer. Most LEMS patients also exhibit the following symptoms (sometimes called autonomic symptoms): dry mouth, constipation, impotence and, decreased sweating, LEMS patients with or without cancer may also undergo significant weight loss. The tendon reflexes are diminished or absent on examination. Hence, in summary, LEMS is often described as a clinical “triad” of proximal muscle weakness, autonomic symptoms and reduced tendon reflexes.2

Autoimmune disorders are caused when the body’s natural defenses against “foreign” or invading organisms (e.g., antibodies) begin to attack healthy tissue for unknown reasons. LEMS occurs because autoantibodies damage the “voltage-gated calcium channels (VGCC)” on the motor nerve membrane at the neuromuscular junction. These channels normally conduct calcium into the nerve resulting in release of a chemical known as acetylcholine. Acetylcholine helps in the communication between nerve cells and muscles and is one of a group of chemicals known as neurotransmitters, which help to transmit nerve impulses. The autoantibodies attack the VGCC resulting in less acetylcholine release. In LEMS cases associated with cancer, it is believed that autoantibodies created against the VGCC on the small-cell lung tumor damage the VGCC on the nerve. It is unknown what causes autoantibody production in cases not associated with cancer. In LEMS cases associated with cancer, affected individuals nearly always have a long smoking history.2

LEMS can be differentiated from myasthenia gravis through electrodiagnostic or through antibody formation. LEMS can be diagnosed when the patient is positive for antibodies against voltage-gated calcium channels (VGCC) unlike myasthenia gravis which as anti-
acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase (MuSK) antibodies. The electrodiagnostic differences between LEMS and myasthenia gravis are shown in the table below:

<table>
<thead>
<tr>
<th></th>
<th>LEMS</th>
<th>Myasthenia gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude of CMAP to a single supramaximal stimulus</td>
<td>Decreased</td>
<td>Normal or near normal</td>
</tr>
<tr>
<td>Postactivation potentiation</td>
<td>Marked increase in CMAP by more than 100%</td>
<td>May be seen, and when present less marked than LEMS</td>
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<tr>
<td>Repetitive nerve stimulation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At slow rates (2-5Hz)</td>
<td>Decremental pattern</td>
<td>Decremental pattern (&gt; 10% decrement in generally considered to be abnormal)</td>
</tr>
<tr>
<td>At fast rates (30-50Hz)</td>
<td>Incremental pattern (over 2-20 times)</td>
<td>May show incremental pattern, but usually less marked than LEMS</td>
</tr>
<tr>
<td>SFEMG</td>
<td>Increased jitter and intermittent impulse blocking, which improve with higher firing rates</td>
<td>Increased jitter an impulse blocking which get worse with higher firing rates</td>
</tr>
<tr>
<td>Microelectrode studies:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEPP amplitudes</td>
<td>Normal</td>
<td>Small or undetectable</td>
</tr>
<tr>
<td>EPP quantal content</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Distribution of EPP amplitudes</td>
<td>Poisson’s distribution</td>
<td>Normal distribution</td>
</tr>
</tbody>
</table>

CMAP: compound muscle action potential; SFEMG: single fiber electromyography; (M)EPP: (miniature) end-plate potential

UpToDate recommends that patients with LEMS who have mild weakness that does not interfere with function can be monitored without use of symptomatic or immunologic therapy.

**Firdapse Efficacy**

The mechanism by which Firdapse (amifampridine) exerts its therapeutic effect in LEMS patients has not been fully elucidated. Amifampridine is a broad-spectrum potassium channel blocker.

The efficacy of Firdapse for the treatment of LEMS was demonstrated in two randomized, double-blind, placebo-controlled discontinuation studies. A total of 64 adults with LEMS (confirmed by either neurophysiology studies or a positive anti-P/Q type voltage-gated calcium channel antibody test. Patients were required to be on an adequate and stable dosage (30 to 80 mg daily) of amifampridine prior to entering the randomized discontinuation phases of both studies.
The two co-primary measures of efficacy in both studies were the change from baseline to the end of the discontinuation period in the Quantitative Myasthenia Gravis (QMG) score and in the Subject Global Impression (SGI) score. The QMG is a 13-item physician-rated categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale, where a score of 0 represents no weakness, and a score of 3 represents severe weakness. Higher scores represent greater impairment. The SGI is a 7-point scale on which patients rated their global impression of the effects of the study treatment on their physical well-being. Lower scores on the SGI represent lower perceived benefit with the study treatment.

A key secondary efficacy endpoint was the clinical global impression improvement (CGI-I) score, a 7-point scale on which the treating physician rated the global impression of change in clinical symptoms. A higher CGI-I score indicates a perceived worsening of clinical symptoms.

**Firdapse Safety**
Firdapse can cause seizures and is contraindicated in patients with a history of seizures. Firdapse is also contraindicated in patients with hypersensitivity to amifampridine phosphate or another aminopyridine.

**Ruzurgi Efficacy**
The efficacy of Ruzurgi for the treatment of LEMS was established by Study 1 (as referred to in prescribing information), a randomized, double-blind, placebo-controlled, withdrawal study. The primary measure of efficacy was the categorization of the degree of change (e.g., greater than 30% deterioration) in the Triple Timed Up and Go test (3UTG) upon withdrawal of active medication, when compared with the time-matched average of the 3UTG assessments at baseline. The 3UTG is a measure of the time it takes a person to rise from a chair, walk 3 meters, and return to the chair for 3 consecutive laps without pause. Higher 3UTG scores represent greater impairment.

The secondary efficacy endpoint was the self-assessment scale for LEMS-related weakness (W-SAS), a scale from -3 to 3 assessing a person’s feeling of weakening or strengthening from baseline. A higher positive W-SAS score indicates a perceived greater improvement of strength.

None of the patients randomized to continue Ruzurgi experienced a greater than 30% deterioration in the final post-dose 3TUG test. In contrast, 72% of those randomized to placebo experienced a greater than 30% deterioration in the final 3TUG test \((p < 0.0001)\).

The W-SAS score showed a significantly greater decrease in patients randomized to placebo \((-2.4)\) than in those who continued treatment with Ruzurgi \((-0.2; p < 0.0001)\), indicating that patients who were randomized to placebo perceived a worsening of weakness compared to those who remained on Ruzurgi.

Safety and effectiveness of Ruzurgi have been established in patients 6 to less than 17 years of age. Use of Ruzurgi in patients 6 to less than 17 years of age is supported by evidence from adequate and well-controlled studies of Ruzurgi in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients 6 to less than 17 years of age.

**Ruzurgi Safety**
Ruzurgi is contraindicated in patients with history of seizures and those with hypersensitivity to amifampridine or other aminopyridine.
References

2. National Organization for Rare Disorders (NORD). Rare Disease Database. Lambert-Eaton Myasthenic Syndrome.
Amifampridine Prior Authorization with Quantity Limit

TARGET AGENT(s)
Firdapse® (amifampridine)
Ruzurgi® (amifampridine)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firdapse (amifampridine)</td>
<td>76000012100320</td>
<td>M, N, O, or Y</td>
<td>8 tablets</td>
</tr>
<tr>
<td>Ruzurgi (amifampridine)</td>
<td>76000012000320</td>
<td>M, N, O, or Y</td>
<td>10 tablets</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent will be approved when ALL of the following are met:

1. The prescriber has submitted information supporting that the patient has a diagnosis of Lambert Eaton myasthenic syndrome (LEMS) confirmed by at least ONE of the following:
   A. Decreased amplitude of compound muscle action potential (CMAP) to a single supramaximal stimulus
   OR
   B. Positive antibody test against voltage-gated calcium channels (VGCC)
   AND
2. The patient has weakness that interferes with normal function
   AND
3. ONE of the following:
   A. The requested agent is Ruzurgi
   OR
   B. ONE of the following:
      i. The patient has tried and had an inadequate response to Ruzurgi
      OR
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to Ruzurgi that is not expected to occur with the requested agent
   AND
4. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis
   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. The requested quantity (dose) does not exceed the program quantity limit

Length of Approval: 6 months

Renewal Evaluation

Target Agent will be approved when ALL of the following are met:
1. The patient has been previously approved for an amifampridine containing agent through the plan’s Prior Authorization process  
   AND
2. The patient has had clinical benefit with an amifampridine containing agent [e.g., improved weakness, improved fatigue, improvement in activities of daily living (ADL)]  
   AND
3. ONE of the following:  
   A. The requested agent is Ruzurgi  
   OR  
   B. The patient has tried and had an inadequate response to Ruzurgi  
   OR  
   C. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to Ruzurgi that is not expected to occur with the requested agent  
   AND
4. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis  
   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent  
   AND
6. The requested quantity (dose) does not exceed the program quantity limit

**Length of Approval:** 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria