Amifampridine Prior Authorization with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
5/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Firdapse® (amifampridine) Tablet	Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients 6 years of age and older		1
Ruzurgi® (amifampridine) Tablet	Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age		2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

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.(3) LEMS 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 and hands, speech and 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 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. In summary, LEMS is often described as a clinical "triad" of proximal muscle weakness, autonomic symptoms and reduced tendon reflexes.(3)

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	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 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.(3) A differential diagnosis of LEMS must be determined due to its similarities in presentation to myasthenia gravis. Diagnosis of LEMS is based on clinical signs and symptoms, electrophysiological studies, and antibody testing. 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.(4) The triad of electrophysiologic abnormalities in LEMS consists of the following: • Diffusely reduced motor amplitudes on motor nerve conduction studies, often less than 50% of the laboratory's lower limits of normal • Decrement with low-frequency stimulation; as opposed to myasthenia gravis, where the decrement is usually maximal at the fourth or fifth stimulation in the train, in LEMS the maximal decrement may occur later in the train • Increment with high-frequency stimulation or facilitation after 10 seconds of maximal voluntary contraction. Increments of more than 100% are very suggestive for LEMS but not specific for LEMS and occur in some cases of botulism and myasthenia gravis The most effective symptomatic treatment in LEMS is 3,4-diaminopyridine (3,4-DAP), also known as amifampridine. Through blocking voltage-gated potassium channels,3,4-DAP prolongs nerve terminal depolarization and increases acetylcholine release. In theory, pyridostigmine should be synergistic with 3,4-DAP but many patients with LEMS have no benefit from pyridostigmine either on its own or in combination with 3,4-DAP.(4)
Firdapse Efficacy(1)	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

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	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.
Ruzurgi Efficacy(2)	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 less than 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 less than 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.

Safety(1,2)	• Firdapse is contraindicated in patients with:
	  ○ A history of seizures
	  ○ A hypersensitivity to amifampridine or another aminopyridine
	• Ruzurgi is contraindicated in patients with:
	  ○ A history of seizures
	  ○ A hypersensitivity to amifampridine or other aminopyridine

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REFERENCES

Number	Reference
1	Firdapse Prescribing Information. Catalyst Pharmaceuticals. September 2022.
2	Ruzurgi Prescribing Information. Jacobus Pharmaceutical Company Inc. April 2020.
3	National Organization for Rare Disorders (NORD). Rare Disease Database. Lambert-Eaton Myasthenic Syndrome.
4	Nicolle MW. Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome. Continuum (Minneap Minn) 2016;22(6): 1978-2005.

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POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
Firdapse	amifampridine phosphate tab	10 MG	M ; N ; O ; Y	N		
Ruzurgi	amifampridine tab	10 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Firdapse	Amifampridine Phosphate Tab 10 MG (Base Equivalent)	10 MG	240	TABS	30	Days				
Ruzurgi	Amifampridine Tab 10 MG	10 MG	300	TABS	30	Days				

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Firdapse	amifampridine phosphate tab	10 MG	Commercial ; HIM ; ResultsRx
Ruzurgi	amifampridine tab	10 MG	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Firdapse	Amifampridine Phosphate Tab 10 MG (Base Equivalent)	10 MG	ResultsRx
Ruzurgi	Amifampridine Tab 10 MG	10 MG	ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The prescriber has provided information supporting that the patient has a diagnosis of Lambert Eaton myasthenic syndrome (LEMS) confirmed by at least ONE of the following: (medical records required) 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. If the patient has an FDA approved indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**

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Module	Clinical Criteria for Approval
	B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient has weakness that interferes with normal function **AND** 4. The patient does NOT have a history of seizures **AND** 5. 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** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months Note: Quantity Limit applies, please see Quantity Limit criteria section below. **Renewal Evaluation** **Target Agent(s)** 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. The patient has not developed a history of seizures while using the requested medication **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 **Length of Approval:** 12 months Note: Quantity Limit applies, please see Quantity Limit criteria section below.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limits** for the **Target Agent(s)** will be approved when the requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** 6 months for initial 12 months for renewal

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