09-J3000-22

Original Effective Date: 04/01/19

Reviewed: 09/11/19

Revised: 10/01/19

Subject: Amifampridine (Firdapse®, Ruzurgi)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Lambert-Eaton myasthenic syndrome (LEMS) is a rare, neuromuscular autoimmune disorder. The disease may be idiopathic or if paraneoplastic, most commonly associated with small cell lung cancer. Autoantibodies to voltage-gated calcium channels (VGCC) on presynaptic nerve terminals reduce the release of acetylcholine (ACh) vesicles which results in progressive muscle weakness. The clinical presentation includes weakness in proximal limbs typically first presenting in the legs and diminished tendon reflexes. Patients also experience disruption of the autonomic system and present with orthostatic hypotension, dry mouth, blurred vision, constipation and difficulty urinating. Testing for autoantibodies and performing neurophysiologic studies aids in diagnosis. Repetitive nerve stimulation (RNS) is used and applies a single supramaximal stimulus to generate a baseline compound muscle action potential (CMAP) followed by another stimulus. In LEMS, the second stimulus typically shows an increase in the CMAP amplitude by more than 100%.

Amifampridine is Food and Drug Administration (FDA) approved for the treatment of LEMS in adults and children age 6 to less than 17 years of age. Amifampridine is a broad spectrum potassium channel blocker that prolongs depolarization of nerve action potentials to increase the open time of VGCC which increases presynaptic calcium levels. The increased calcium influx enhances ACh release which binds to muscle receptors and results in improved muscle function.

Amifampridine(Firdapse®) was evaluated in two randomized, double-blind, placebo-controlled discontinuation studies in 64 adults with LEMS. LEMS was confirmed based on neurophysiology studies or a positive anti-P/Q type voltage-gated calcium channel antibody test. Patients were required to be on a stable dosage of amifampridine ranging from 30 to 80 mg daily prior to a discontinuation phase. Efficacy was measured by the change in Quantitative Myasthenia Gravis (QMG) score (range 0-39, higher score indicates worsening) and the Subject Global Impression (SGI) score (range 0-7, lower score indicates worsening). The clinical global impression improvement (CGI-I) score (range 0-7, higher score indicates worsening) was evaluated as a secondary endpoint.

In study 1, 38 patients were randomized to continue amifampridine (n=16) or titrate down to a placebo (n=22) over 7 days. Patients were either treatment experienced with amifampridine or if treatment naïve had documented proximal muscle weakness and a QMG score of 5 or greater prior to enrollment. Patients were allowed to continue use of stable peripherally acting cholinesterase inhibitors or oral immunosuppressants. The change from baseline to day 14 in QMG score was significantly less with amifampridine as compared to placebo (0.4 vs 2.2; least square mean (LEM) difference -1.7, p=0.045) indicating less impairment with continued treatment. The change from baseline to day 14 in SGI score was significantly higher with amifampridine as compared to placebo (-0.8 vs -2.6; LSM difference 1.8, p=0.003) indicating sustained benefits with continued treatment. The CGI-I also demonstrated a higher score in the placebo group to indicate perceived worsening as compared to amifampridine (LSM difference -1.1, p=0.02). Worsening of QMG, SGI, and CGI-I scores also occurred following discontinuation of amifampridine in the placebo group when assessed at day 4 in the 13 patients enrolled in the placebo arm in study 2. The most common adverse reactions included paresthesia, upper respiratory tract infection, abdominal pain, back pain, nausea, diarrhea, headache elevated liver enzymes, hypertension and muscle spasms.

Amifampridine (Ruzurgi) was also evaluated in a randomized, double-blind, placebo-controlled withdrawal study. Patients were randomized to continue treatment with amifampridine or switch to placebo over a 3-day downward titration period. Following the titration period, patients either remained on amifampridine or placebo for 16 more hours. Efficacy was assessed 2 hours after the last dose of the downward titration period. The primary efficacy endpoint was the degree of change (greater than 30% deterioration) in the Triple Timed Up and Go test (3TUG) upon medication withdrawal as compared to assessment at baseline (higher score represent greater impairment). The secondary efficacy endpoint was the self-assessment scale for LEMS-related weakness (W-SAS, scale from -3 to 3 and higher score is greater improvement of strength). The 32 enrolled patients had a median age of 56 years (range 23 – 83 years) and were allowed to use stable doses of peripherally-acting cholinesterase inhibitors or oral immunosuppressants. None of the patients randomized to amifampridine experienced a greater than 30% deterioration in the final 3TUG test as compared to 13/18 (72%) in the placebo group (p<0.0001). The W-SAS score was lower in the placebo group which indicated a greater worsening of weakness as compared to those on amifampridine (-2.4 vs -0.2, p<0.0001). The most common adverse events include paresthesia, abdominal pain, dyspepsia, dizziness, nausea, back pain, hypothesia and muscle spasms.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of amifampridine (Ruzurgi) **meets the definition of medical necessity** for the following indications when the specific criteria are met:

1. Lambert-Eaton myasthenic syndrome (LEMS)
    A. Member meets **ONE** of the following:
        i. Positive anti-P/Q type voltage-gated calcium channel antibody test – documentation must be submitted

ii. Repetitive nerve stimulation testing demonstrates a compound muscle action potential (CMAP) that increases at least 2-fold after maximum voluntary contraction of the tested muscle – documentation must be submitted

B. The member has proximal muscle weakness associated with LEMS

C. The member does not have a history of seizures

D. The prescriber is a board certified (or board eligible) neurologist or the prescriber has consulted with a specialist in the area of the patient's diagnosis

E. The member is 6 years of age or older

F. The dose does not exceed the following using the fewest number of tablets per day to permit up to five times per day dosing:

a. 45 kg or more: 100 mg daily

b. Less than 45 kg: 50 mg daily

Approval duration: 6 months

Continuation of amifampridine (Ruzurgi) **meets the definition of medical necessity** for the treatment of LEMS when **ALL** of the following criteria are met:

1. An authorization or reauthorization for amifampridine (Ruzurgi) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of LEMS, **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has a beneficial response to treatment (e.g., improvement in QMG, stabilization of Triple Timed Up and Go test - 3TUG) – documentation must be provided
3. The dose does not exceed the following using the fewest number of tablets per day to permit up to five times per day dosing:
    a. 45 kg or more: 100 mg daily
    b. Less than 45 kg: 50 mg daily

Approval duration: 1 year

Initiation of amifampridine (Firdapse) **meets the definition of medical necessity** for the following indications when the specific criteria are met:

1. Lambert-Eaton myasthenic syndrome (LEMS)
    A. Member meets ONE of the following:
        i. Positive anti-P/Q type voltage-gated calcium channel antibody test – documentation must be submitted
        ii. Repetitive nerve stimulation testing demonstrates a compound muscle action potential (CMAP) that increases at least 2-fold after maximum voluntary contraction of the tested muscle – documentation must be submitted
    B. The member has proximal muscle weakness associated with LEMS
    C. The member does not have a history of seizures
    D. The prescriber is a board certified (or board eligible) neurologist or the prescriber has consulted with a specialist in the area of the patient's diagnosis
    E. The member is 18 years of age or older

F. The member has tried and had intolerable adverse effects to amifampridine (Ruzurgi) and ALL of the following must be submitted:

   i. The specific intolerance(s) to Ruzurgi and rationale for use of Firdapse must be provided

   ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

   iii. Completed Naranjo Adverse Drug reaction probablility scale - https://livertox.nih.gov/Naranjoassessment.pdf

G. The dose does not exceed 80 mg daily using the fewest number of tablets per day to permit three to four times per day dosing

Approval duration: 6 months

Continuation of amifampridine (Firdapse) **meets the definition of medical necessity** for the treatment of LEMS when **ALL** of the following criteria are met:

1. An authorization or reauthorization for amifampridine (Firdapse) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of LEMS, **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has a beneficial response to treatment (e.g., improvement in QMG, stabilization of Triple Timed Up and Go test - 3TUG) – documentation must be provided
3. The member has tried and had intolerable adverse effects to amifampridine (Ruzurgi) and ALL of the following must be submitted:

   c. The specific intolerance(s) to Ruzurgi and rationale for use of Firdapse must be provided

   d. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

   e. Completed Naranjo Adverse Drug reaction probablility scale - https://livertox.nih.gov/Naranjoassessment.pdf

4. The dose does not exceed 80 mg daily using the fewest number of tablets per day to permit three to four times per day dosing

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Lambert-Eaton myasthenic syndrome in adults (Firdapse): starting dose is 15 mg to 30 mg oral daily y in divided doses (3-4 times daily). The dose can be increased by 5 mg daily every 3 to 4 days to a maximum of 80 mg daily (maximum single dose is 20 mg). If a dose is missed do not take double or extra doses.
- Lambert-Eaton myasthenic syndrome in pediatrics age 6 to less than 17 years (Ruzurgi): **45Kg or more:** starting dose is 15 mg to 30 mg oral daily taken oral daily in divided doses. The dose can be increased by 5 mg to 10 increments and divided up to 5 times daily. The maximum single dose is 30 mg and maximum daily is 100 mg. **Less than 45Kg:** starting

dose is 7.5 mg to 15 mg oral daily in divided doses. The dose can be increased by 2.5 mg to 5 mg increments and divided up to 5 times daily. The maximum single dose is 15 mg an maximum daily is 50 mg. If a dose in less than 5 mg increments is required, or if the patient has difficulty swallowing, a 1 mg/ml suspension can be prepared.

Dose Adjustments

- Renal impairment (CrCl 15 – 90 mL/min) and 45 kg or more: 15 mg daily, in 3 divided doses
- Renal impairment (CrCl 15 – 90 mL/min) and less than 45 kg: 7.5 mg daily, in 3 divided doses
- Hepatic impairment and 45 kg or more: 15 mg daily, in 3 divided doses
- Hepatic impairment and less than 45 kg: 7.5 mg daily, in 3 divided doses
- N-acetyltrasferase 2 (NAT2) poor metabolizers and 45 kg or more: 15 mg daily, in 3 divided doses
- N-acetyltrasferase 2 (NAT2) poor metabolizers and less than 45 kg: 7.5 mg daily, in 3 divided doses

Drug Availability

- 10 mg scored tablet

PRECAUTIONS:

Boxed Warning

- none

Contraindications

- History of seizures
- Hypersensitivity to amifampridine or another aminopyridine

Precautions/Warnings

- Seizures: Consider discontinuation or dose-reduction in patients who have a seizure while on treatment.
- Hypersensitivity reactions: Discontinue for anaphylaxis.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G73.1	Lambert Eaton syndrome in neoplastic disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage:

- No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

none

RELATED GUIDELINES:

Immune Globulin, 09-J0000-06

OTHER:

Table 3: Quantitative Myasthenia Gravis Score for Disease Severity

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
(1) Double vision on lateral gaze, seconds	61	11-60	1-10	Spontaneous	
(2) Ptosis on upward gaze, seconds	61	11-60	1-10	Spontaneous	
(3) Weakness of facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
(4)Swallowing water	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)	
(5) Speech after counting aloud	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	

from 1-50					
(6) Ability to keep right arm outstretched, seconds	240	90-239	10-89	0-9	
(7) Ability to keep left arm outstretched, seconds	240	90-239	10-89	0-9	
(8) Vital capacity as percent of predicted	Greater or equal to 80	65-79	50-64	Less than 50	
(9) Right hand grip strength, kgW	Men – 45 or greater Women – 30 or greater	Men – 15-44 Women – 10-29	Men – 5-14 Women – 5-9	Men –0-4 Women – 0-4	
(10) Left hand grip strength, kgW	Men – 45 or greater Women – 30 or greater	Men – 15-44 Women – 10-29	Men – 5-14 Women – 5-9	Men –0-4 Women – 0-4	
(11) Ability to keep head lifted when lying supine, seconds	120	30-119	1-29	0	
(12) Ability to keep the right leg outstretched, seconds	100	31-99	1-30	0	
(13) Ability to keep the left leg outstretched, seconds	100	31-99	1-30	0	
Total QMG Score:					

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2019 [cited 2019 June 24]. Available from: http://www.clinicalpharmacology.com/.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2019 June 24]. Available from: http://www.thomsonhc.com/.
3. Firdapse (amifampridine)[package insert]. Catalyst Pharmaceuticals, Inc. Coral Gables, FL. November 2018.
4. Hulsbrink R, Hashemolhosseini. Lambert-Eaton myasthenic syndrome – Diagnosis, pathogenesis and therapy. Clinical Neurophysiology. 2014: 125: 2328-2336.
5. Oh SJ, Shcherbakova N, Kostera-Pruszczyk A et al. Amfampridine Phosphate is effective and safe in a phase 3 clinical trial in LEMS. *Muscle Nerve.* 2016; 53: 717- 725.
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2019 [2019 Jan 28]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
7. Ruzurgi (amifampridine)[package insert]. Jacobus Pharmaceutical Company, Inc. Plainsboro, NJ. May 2019.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 07/10/19.

GUIDELINE UPDATE INFORMATION:

04/01/19	New Medical Coverage Guideline.
10/01/19	Review and revision to guideline; consisting of updating position statement, description, dosing and references.