

amifampridine (Firdapse[®])

Policy # 00676

Original Effective Date: 08/14/2019

Current Effective Date: 09/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider amifampridine (Firdapse[®])[‡] for the treatment of Lambert Eaton myasthenic syndrome (LEMS) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for amifampridine (Firdapse) for the treatment of LEMS will be considered when the following criteria are met:

- Patient has a diagnosis of Lambert-Eaton Myasthenic Syndrome (LEMS) confirmed by ONE of the following:
 - Reproducible post-exercise increase in compound muscle action potential (CMAP) amplitude of at least 60% compared with pre-exercise baseline value or a similar increment on high-frequency repetitive nerve stimulation without exercise; OR
 - Positive anti-P/Q-type voltage-gated calcium channels antibody testing; AND
- Patient is experiencing moderate to severe weakness that interferes with function; AND
- Patient does NOT have a history of seizures.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of amifampridine (Firdapse) when the patient selection criteria are not met to be **investigational**.*

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Background/Overview

Amifampridine (Firdapse) is a potassium channel blocking drug indicated for the treatment of patients with Lambert-Eaton myasthenic syndrome (LEMS). It contains amifampridine, [also known as 3,4-diaminopyridine (3,4-DAP)], a product that is available for this indication in Europe and was previously available in the U.S. as a base for use in compounding. The recommended dosage for adults and pediatric patients weighing 45 kg or more (regardless of age) is 15 mg to 30 mg daily by mouth in divided doses (3 to 5 times daily). The dosage can be increased by 5 mg/day every 3 or 4 days to a maximum dose of 100 mg/day. The recommended dosage for pediatric patients weighing less than 45 kg is 5 mg to 15 mg daily, in divided doses (3 to 5 times daily). This dosage can be increased in 2.5 mg increments to a maximum daily dosage of 50 mg/day. Amifampridine is contraindicated in patients with a history of seizures due to an increased incidence of seizures in patients taking this drug at the recommended doses.

Lambert-Eaton Myasthenic Syndrome is a rare, autoimmune disorder affecting the connection between nerves and muscles and causing proximal muscle weakness, autonomic dysfunction, and areflexia. Presenting symptoms include leg weakness (60%), generalized weakness (18%), muscle pain or stiffness (5%), dry mouth (5%), arm weakness (4%), diplopia (4%), and dysarthria (2%). Weakness normally spreads proximally (most common in the upper arms and legs) to distally (involving feet and hands) and from the posterior towards the head, finally reaching the oculobulbar region. This is in contrast to myasthenia gravis, in which weakness typically starts in the head and then descends. The characteristic weakness is thought to be caused by antibodies generated against the P/Q-type voltage gated calcium channel (VGCC) present on presynaptic nerve terminals and by diminished release of acetylcholine. It is estimated that LEMS affects 3 people per million worldwide. More than 50% of cases are associated with small cell lung cancer (SCLC) which expresses functional VGCC. The diagnosis of LEMS is confirmed by electrodiagnostic studies including repetitive nerve stimulation and anti-P/Q-type VGCC antibody testing.

There is no cure for LEMS. Treatment is directed at decreasing the autoimmune response through the use of steroids, plasmapheresis, or high-dose intravenous immunoglobulin (IVIG) or improving the transmission of the disrupted electrical impulses by using medications such as an aminopyridine (i.e., amifampridine) or pyridostigmine bromide. For patients with SCLC, treatment of the cancer is the first priority. Guanidine hydrochloride, a potassium channel blocker, was first approved in 1939 and is the only other FDA-approved treatment for the reduction of the symptoms of muscle weakness and easy fatigability associated with LEMS. Data with guanidine in LEMS are limited and approval occurred in an era in which rigorous efficacy standards were not in place. The potential for bone marrow suppression and renal impairment further narrow the role of guanidine in LEMS. The anticholinesterase agent pyridostigmine is used off-label for the treatment of LEMS. Pyridostigmine slows the breakdown of acetylcholine at the neuromuscular junction and thereby improves neuromuscular transmission and increases muscle strength.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Firdapse was approved in November 2018 for the treatment of LEMS in adults. The indication was expanded to include pediatric patients 6 years of age and older in September 2022.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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 (age 21 to 88 years) with a confirmed diagnosis of LEMS (based on either neurophysiology studies or a positive anti-P/Q type voltage-gated calcium channel antibody test) were enrolled. Patients were required to be on an adequate and stable dosage (30-80 mg daily) of amifampridine phosphate 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 (total score 0-39). 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.

Study 1 included 38 patients who were randomized from an open-label run-in phase to continue treatment with Firdapse (n = 16) or to a downward titration to placebo (n = 22) over 7 days. Following the downward titration period, patients remained on blinded Firdapse or placebo for 7 more days. Efficacy was assessed at Day 14 of the double-blind period. Patients were allowed to use stable dosages of peripherally acting cholinesterase inhibitors or oral immunosuppressants. Twenty-six percent of patients randomized to Firdapse were receiving cholinesterase inhibitors, versus 36% in the placebo group, and 28% of patients randomized to Firdapse were receiving oral immunosuppressant therapies versus 34% in the placebo group. During the double-blind period, the QMG scores tended to worsen in both treatment groups, but there was significantly greater worsening in the placebo group than in the Firdapse group (treatment difference of -1.7 [p = 0.045]). Similarly, the SGI score tended to worsen in both treatment groups, but there was significantly greater worsening in the placebo group than in the Firdapse group (treatment difference of 1.8 [p = 0.003]).

Study 2 included 26 patients on stable treatment with Firdapse who were randomized 1:1 in a double-blind fashion to either continue treatment with Firdapse (n = 13) or change to placebo (n = 13) for 4 days. Efficacy was assessed at the end of the 4-day double-blind discontinuation period. Patients were allowed to use stable doses of peripherally acting cholinesterase inhibitors or corticosteroids. Sixty-one percent of patients randomized to Firdapse were receiving cholinesterase inhibitors, versus 54% of patients randomized to placebo. Corticosteroid use was similar between Firdapse and placebo (8%). Patients with recent use of immunomodulatory therapies (e.g., azathioprine, mycophenolate, cyclosporine), rituximab, IVIG, and plasmapheresis were excluded from the study.

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From baseline to Day 4, there was significantly greater worsening in the QMG score in the placebo group than in the Firdapse group (treatment difference of -6.54 [p = 0.0004]), and also significantly greater worsening in the SGI score in the placebo group than in the Firdapse group (treatment difference of 2.95 [p = 0.0003]).

References

1. Firdapse [package insert]. Catalyst Pharmaceuticals, Inc. Coral Gables, FL. Updated May 2024.
2. Amifampridine Products Prior Authorization Policy. Express Scripts. June 2019.
3. Firdapse Drug Evaluation. Express Scripts. December 2018.

Policy History

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08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. New policy.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. Removed Ruzurgi from policy due to its removal from the market.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/07/2025	Medical Policy Committee review
08/13/2025	Medical Policy Implementation Committee approval. Minor updates to background information. Coverage eligibility unchanged.
08/12/2026	Pre Pharmacy & Therapeutics Committee review.
08/19/2026	Pharmacy & Therapeutics Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2027

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

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whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.