amifampridine (Firdapse®‡, Ruzurgi™‡)

Policy # 00676
Original Effective Date: 08/14/2019
Current Effective Date: 09/14/2020

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.

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®‡, Ruzurgi™‡)‡ for the treatment of Lambert Eaton myasthenic syndrome (LEMS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for amifampridine (Firdapse, Ruzurgi) 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; AND
- If the request is for Firdapse, the patient has tried and failed (e.g. intolerance or inadequate response) Ruzurgi unless there is clinical evidence or patient history that suggests Ruzurgi will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the use of amifampridine (Firdapse) when the patient has not tried and failed amifampridine (Ruzurgi) is considered to be **not medically necessary.****

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, Ruzurgi) when the patient selection criteria are not met (except those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Amifampridine (Firdapse, Ruzurgi) is a potassium channel blocking drug indicated for the treatment of patients with Lambert-Eaton myasthenic syndrome (LEMS). Both products contain 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 U.S. Food and Drug Administration (FDA) has approved the two products for use in two different age groups. Firdapse is approved for use in adults and Ruzurgi is approved for patients 6 years to less than 17 years of age. However, it should be noted that both drugs were approved based on studies in adult patients and can be considered therapeutically equivalent. The recommended dosage of both products for patients weighing 45 kg or more (regardless of age) is 15 mg to 30 mg daily by mouth in divided doses (3 to 4 times daily). The dosage can be increased by 5 mg/day every 3 or 4 days to a maximum dose of 80 mg/day. The recommended dosage of Ruzurgi for patients weighing less than 45 kg is 7.5 mg to 15 mg daily, in divided doses (3 to 4 times daily). This dosage can be increased in 2.5 mg to 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 (LEMS) 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 LMS. 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 Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Ruzurgi was approved in May 2019 for the treatment of Lambert-Eaton myasthenic syndrome in patients 6 to less than 17 years of age.

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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, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Firdapse

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. 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]).

Ruzurgi
The efficacy of Ruzurgi for the treatment of LEMS was established by Study 1, a randomized, double-blind, placebo-controlled, withdrawal study. It included 32 patients with a diagnosis of LEMS confirmed by documentation and an independent neurologist review. Patients were required to be on an adequate and stable dosage (30 mg to 100 mg daily for at least 3 months) of Ruzurgi prior to entering the study. The primary measure of efficacy was the categorization of the degree of change in the Triple Timed Up and Go test (3TUG) upon withdrawal of active medication, when compared with the time-matched average of the 3TUG assessments at baseline. The 3TUG 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 3TUG scores represent greater impairment.

After an initial open-label run-in phase, 32 patients were randomized to continue treatment with Ruzurgi (n=14) or switch to placebo (n=18) over a 3-day downward titration period. Following the downward titration period, patients remained on blinded Ruzurgi or placebo for 16 more hours. Efficacy was assessed 2 hours after the last dose of the downward titration period. Patients were

allowed to use stable dosages of peripherally-acting cholinesterase inhibitors or oral immunosuppressants. Seventy-nine percent of patients randomized to Ruzurgi were receiving cholinesterase inhibitors, versus 83% in the placebo group, and 29% of patients randomized to Ruzurgi were receiving an immunosuppressant therapy, versus 39% in the placebo group. 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 ($p<0.0001$). Patients who were randomized to placebo returned to baseline after restarting Ruzurgi.

Although no pediatric patients were included in Study 1, safety data in pediatric patients aged 6 to less than 17 years was evaluated in patients treated in expanded access programs. There were 15 patients in this age group who received Ruzurgi, of whom 9 received Ruzurgi for at least 1 year. Adverse reactions reported in pediatric patients 6 to less than 17 years of age were similar to those seen in adult patients.

References

1. Firdapse [package insert]. Catalyst Pharmaceuticals, Inc. Coral Gables, FL. Updated November 2018.
2. Ruzurgi [package insert]. Jacobus Pharmaceutical Company, Inc. Princeton, NJ. Updated May 2019.
3. Amifampridine Products Prior Authorization Policy. Express Scripts. June 2019.
4. Firdapse Drug Evaluation. Express Scripts. December 2018.

Policy History

Original Effective Date: 08/14/2019
Current Effective Date: 09/14/2020
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.
Next Scheduled Review Date: 08/2021

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*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 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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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.