BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

FIRDAPSE® (amifampridine phosphate) oral

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Firdapse (amifampridine phosphate) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist.
2. Individual is 18 years of age or older.
3. Individual has a confirmed diagnosis of Lambert-Eaton myasthenic syndrome.
4. Individual has moderate to severe proximal muscle weakness that interferes with daily function.
5. Individual has a baseline Quantitative Myasthenia Gravis (QMG) test score of 5 or more.

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6. The individual has received and completed **ONE** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Individual is positive for anti-P/O type voltage-gated calcium channel (VGCC)
    b. Electrophysiologic studies such as repetitive nerve stimulation abnormalities with **all** of the following results:
        i. Low compound muscle action potential (CMAP)
        ii. A decrement of > 10% at low frequency (1-5Hz)
        iii. An increment of > 100% after maximum voluntary contraction or at high frequency (50Hz)

7. Individual does not have end-stage renal disease (creatinine clearance < 15 mL/min).

8. Individual is not on dialysis.

9. Will not be used with Ampyra (dalfampridine).

10. There are **NO** FDA-label contraindications, such as:
    a. History of seizures
    b. Hypersensitivity to amifampridine or another aminopyridine such as Ampyra (dalfampridine)

Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Firdapse (amifampridine phosphate) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist.

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains **ONE** of the following:
        i. At least a 2.6 units or more improvement in QMG score
        ii. At least a 20% improvement in Triple Timed Up and Walk test (3TUG)
        iii. At least a 60% increase in CAMP
    b. No evidence of disease progression
    c. Functionality retained in most activities of daily living

3. Individual has been adherent with the medication.

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as Seizures

5. Will not be used in end-stage renal disease (creatinine clearance < 15 mL/min).

6. Will not be used in an individual on dialysis.

7. Will not be used with Ampyra (dalfampridine).

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Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Description:

Firdapse (amifampridine phosphate) and Ruzurgi (amifampridine) are broad spectrum voltage-gated potassium channel blockers indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. Amifampridine is also known as 3,4-diaminopyridine (3,4-DAP).

LEMS is a disorder of the neuromuscular junction (NMJ), characterized by slowly progressive proximal muscle weakness, depressed or absent deep tendon reflexes, and autonomic dysfunction. LEMS is caused by antibodies against the voltage-gated calcium channel (VGCC) at the pre-synaptic side of the muscle endplate. The antibodies inhibit acetylcholine release and cause neuromuscular transmission (NMT) failure and muscle weakness.

Antibodies to peripheral nerve P/Q-type VGCC antibodies are present in the serum of at least 85-90% of LEMS patients. These antibodies cause a downregulation of VGCC, lowering the amount of presynaptic calcium and thereby reducing the quantal release of acetylcholine. Other antibody targets such as synaptotagmin and presynaptic M1 muscarinic acetylcholine receptors may be involved in the remaining 15% of LEMS patients.

LEMS is characterized by ascending muscle weakness starting in the proximal lower limb muscles and is associated with autonomic dysfunction. In 50-60% of the patients with LEMS a small cell lung carcinoma (SCLC) will be found. The diagnosis of LEMS almost invariably precedes the discovery of SCLC. Consequently, a diagnosis of LEMS should prompt a vigorous screening for SCLC with treatment of the tumor an essential component of therapy. The prognosis of LEMS is strongly affected by the association with SCLC. Life expectancy depends on the presence and treatment of the lung cancer.

The diagnosis of LEMS is centered on clinical signs and symptoms, electrophysiological studies, and antibody testing. The electrophysiological study of choice is the repetitive nerve stimulation (RNS) test. The amplitude of the first compound muscle action potential (CMAP) is low in LEMS and becomes lower at low stimulation frequencies. A decrease of CMAP amplitude of at least 10% is considered abnormal. To differentiate LEMS from myasthenia gravis (MG) a high frequency stimulation or a post-exercise stimulation is performed. An increase in CMAP amplitude higher than 100% is considered abnormal in LEMS. An abnormal single fiber EMG (SFEMG) can confirm a disorder of the neuromuscular junction but is nonspecific.

Treatment for LEMS is mainly symptomatic. Symptomatic therapies aim to increase the concentration of acetylcholine at the muscle endplate. Acetylcholinesterase inhibitors, such as pyridostigmine, were the first drugs used for the improvement of symptoms. The mechanism of action of increasing synaptic acetylcholine was the proposed benefit for their use. They are not used as first line therapy due to having only a marginal effective, but they can be used as add-on therapy.

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Guanidine hydrochloride was the first agent that showed a benefit in the symptomatic relief of LEMS. Guanidine hydrochloride can increase the concentration of free intracellular calcium by blocking the respiratory chain and potassium channels, prolong the action potential at the nerve terminal, or facilitate calcium channels. Studies have demonstrated that guanidine enhances the release of acetylcholine. Guanidine has been shown to improve electromyographic parameters and muscle strength effectively in multiple case reports. Side effects include bone marrow depression and renal failure. Initial dosage is 10-15 mg/kg per day in 3 or 4 divided doses with gradual increase to 35 mg/kg per day or up to the development of side effects.

Amifampridine (3,4-diaminopyridine) blocks presynaptic potassium channels, in so doing it prolongs the action potential and increases presynaptic calcium concentrations. It has been shown to be more effective than acetylcholinesterase inhibitors. Amifampridine can cause seizures. Seizures have been observed in patients without a history of seizures taking amifampridine at the recommended doses, at various times after initiation of treatment. Seizures may be dose dependent

Immunotherapy is used in more severely affected patients. Treatment recommendations for conventional immunosuppression are similar to the recommendations for MG. Prednisolone plus a steroid-sparing agent, such as azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate, is used. Plasmapheresis can stabilize the patient in a LEMS crisis. Alternatively, intravenous immunoglobulins have been shown to improve limb strength. Immunosuppression is only recommended for patients in whom symptomatic treatment is not sufficient.

Patients with LEMS who have mild weakness that does not interfere with daily function can be monitored without the use of symptomatic or immunologic therapy. For patients with moderate or severe weakness that does interfere with daily function amifampridine is suggested as first choice treatment. If amifampridine is not tolerated or is unavailable, low-dose guanidine with or without pyridostigmine could be considered.

Other autoimmune neurotransmission disorders include MG and neuromyotonia. MG is caused by autoantibodies against components of the post-synaptic neuromuscular junction. The autoimmune attack at the muscle endplate leads to NMT failure and muscle weakness. Neuromyotonia (or peripheral nerve hyper-excitability; Isaacs' syndrome) is caused by antibodies to nerve voltage gated potassium channels (VGKC) that produce nerve hyper-excitability and spontaneous and continuous skeletal muscle over-activity presenting as twitching and painful cramps and stiffness.

Definitions:

Criteria for diagnosis of LEMS:

Clinical features should be present (proximal muscle weakness is required), combined with voltage-gated calcium channel (VGCC) antibodies **OR** repetitive nerve stimulation abnormalities, **or** both

Clinical features

- Proximal muscle weakness – required
- Autonomic symptoms
- Reduced tendon reflexes

Voltage-gated Calcium Channel antibodies (VGCC)
Repetitive nerve stimulation abnormalities

- Low compound muscle action potential (CMAP)
- And decrement > 10% at low frequency (1-5Hz)

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- And increment > 100% after maximum voluntary contraction or at high frequency (50Hz)

Quantitative Myasthenia Gravis (QMG) score:

A 13-item physician-rated categorical scale assessing muscle weakness
Each item is assessed on a 4-point scale: score of 0 = no weakness and a score of 3 = severe weakness
Total score can range: 0-39
Higher scores represent greater impairment
More than 2.6 units of change in QMG score is of clinical significance

Quantitative Myasthenia Gravis (QMG) Test					
Test Item Weakness	**None**	**Mild**	**Moderate**	**Severe**	**Score**
Grade	**0**	**1**	**2**	**3**	
Double vision (lateral gaze), sec	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze), sec	60	11-59	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, no resistance	Incomplete	
Swallowing 4 oz. water	Normal	Minimal coughing or throat clearing	Severe coughing, choking or nasal regurgitation	Cannot swallow	
Speech following counting aloud 1-50 (onset of dysarthria)	None @ #50	Dysarthria @ #30-49	Dysarthria @ #10-29	Dysarthria @ #9	
Right arm outstretched (90° sitting), sec	240	90-239	10-89	0-9	
Left arm outstretched (90° sitting), sec	240	90-239	10-89	0-9	
Forced vital capacity	≥ 80%	65-79%	50-64%	< 50%	
Right hand grip (Kg) Male Female	 ≥ 45 ≥ 30	 15-44 10-29	 5-14 5-9	 0-4 0-4	
Left hand grip (Kg) Male Female	 ≥ 35 ≥ 25	 15-34 10-24	 5-14 5-9	 0-4 0-4	
Head lifted (45° supine), sec	120	30-119	1-29	0	
Right leg outstretched (45-50° supine), sec	100	31-99	1-30	0	
Left leg outstretched (45-50° supine), sec	100	31-99	1-30	0	
Total Score					
Total score can range: 0-39 Higher scores represent greater impairment More than 2.6 units of change in QMG score is of clinical significance					

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Triple Timed Up and Walk Test (3TUG):

The 3TUG is a functional mobility test that requires a patient to stand up from a straight-backed armchair, walk 3 meters, turn around, walk back, and sit down in the chair. A modification of this is where the individual performs the test 3 times without pause, and the measurement is the average time required to complete each of the 3 repetitions. Higher 3TUG scores represent greater impairment. Based upon literature reports that a significant change in gait for a similar walk-test is an increase in time of more than 20%. This was incorporated as a secondary endpoint used in the NCT02970162 clinical trial of Firdapse (amifampridine).

Activities of daily living (ADL):

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

Self-care ADL:

Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

Resources:

Firdapse (amifampridine phosphate) product information, revised by Catalyst Pharmaceuticals, Inc. 03-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 22, 2022.

Ruzurgi (amifampridine) product information, revised by Jacobus Pharmaceutical Company, Inc. 04-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 15, 2021. Discontinued on 02-01-2022

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