BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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FIRDAPSE® (amifampridine phosphate) oral
RUZURGI® (amifampridine) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

FIRDAPSE® (amifampridine phosphate) oral
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Criteria:

- **Criteria for initial therapy:** Firdapse (amifampridine phosphate) and Ruzurgi (amifampridine) is considered ***medically necessary*** and will be approved when **ALL** of 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's age is **ONE** of the following:
     a. **For Firdapse (amifampridine)**: 18 years of age or older
     b. **For Ruzurgi (amifampridine)**: 6 to < 17 years of age or older

  3. 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

  6. **ONE** of the following baseline tests have been completed before initiation of treatment with continued monitoring 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 has a failure, contraindication, or intolerance to Guanidine

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

  9. Will not be used in an individual on dialysis

  10. Will not be used with Ampyra (dalfampridine)

  11. There are **NO** contraindications
      a. Contraindications include:
         i. History of seizures
         ii. Hypersensitivity to amifampridine or another aminopyridine such as Ampyra (dalfampridine)

Initial approval duration: 3 months

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- **Criteria for continuation of coverage (renewal request):** Firdapse (amifampridine phosphate) and Ruzurgi (amifampridine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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 responded while on therapy
    a. Response is defined as **ALL** of the following:
        i. Achieved and maintains **ONE** of the following:
            1. At least a 2.6 units or more improvement in QMG score
            2. At least a 20% improvement in Triple Timed Up and Walk test (3TUG)
            3. At least a 60% increase in CAMP
        ii. No evidence of disease progression
        iii. 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 level 4 adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. 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)

8. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Firdapse (amifampridine phosphate) and Ruzurgi (amifampridine) are broad spectrum voltage-gated potassium channel blocker 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.

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 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)
- 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 significant

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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 significant					

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).

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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 accessed 04-24-19 at DailyMed

Ruzurgi (amifampridine) product information accessed 07-19-19 at DailyMed

UpToDate: lambert-Eaton myasthenic syndrome. Current through March 2019.

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Skeie GO, Apostolski S, Evoli A, et al.: Guidelines for treatment of autoimmune neuromuscular transmission disorders. European Federation of Neurological Societies (EFNS) Guideline. European Journal of Neurology 2010:17, 893–902

Keogh M, Sedehizadeh S, Maddison P: Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database of Systematic Reviews 2011, Issue 2. Art. No.: CD003279. DOI: 10.1002/14651858.CD003279.pub3.

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Sanders DB, Massey J, Sanders LL, Edwards LJ: A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. Neurology 2000 Feb 8; 54 (3):603