Amifampridine (Firdapse®, Ruzurgi®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO004

Description
Amifampridine (Firdapse, Ruzurgi) are orally administered, broad-spectrum potassium channel blockers.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
amifampridine (Firdapse)	10 mg tablets	LEMS	240 tablets/30 days	194155
amifampridine (Ruzurgi)	10 mg tablets	LEMS	240 tablets/30 days	206714

Initial Evaluation

I. Amifampridine (Firdapse, Ruzurgi) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of **Lambert-Eaton Myasthenic Syndrome (LEMS)**; **AND**
      a. Documentation of a confirmatory diagnostic test:
         i. Repetitive Nerve Stimulation (RNS); **OR**
         ii. Positive anti-P/Q type voltage-gated calcium channel antibody test;

   AND
   B. Prescribed by or in consultation with a neurologist; **AND**
   C. Documentation of an adequate trial and failure or intolerance to one of the following, or contraindication to both of the following:
      1. Pyridostigmine or IVIG; **AND**
   D. If the request is for Firdapse, documentation of an adequate trial and failure or intolerance to Ruzurgi.

II. Amifampridine (Firdapse, Ruzurgi) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:

A. Inflammatory muscle disease
B. Limb-girdle muscular dystrophy
C. Myasthenia gravis
D. Congenital myasthenic syndrome
E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

Renewal Evaluation

I. Provider attestation of clinical improvement of symptoms.

Supporting Evidence

I. LEMS is a rare presynaptic disorder of neuromuscular transmission in which the release of acetylcholine is impaired.
   - Disruption of a subset of P/Q-type CA2+ channels causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction.
   - Major clinical presentation is progressive proximal muscle weakness.
   - Forty to 60% of LEMs cases are paraneoplastic, involving and correlated with a [usually new] cancer diagnosis.
   - Remaining patients with autonomic LEMS and without cancer, expect normal longevity.
   - Incidence of LEMS is estimated to be approximately 156 to 244 new cases per year in the United States, with a total prevalence of 2.3 to five cases per million people.

II. Amifampridine (3,4-diaminopyridine) results in an increased release of acetylcholine via potassium channel blockade. Guanidine is approved for the treatment of LEMS, however, is associated with a high-level of toxicity and adverse effects. Pyridostigmine is known to be less toxic overall and is sometimes taken as monotherapy or in conjunction with guanidine. Use of pyridostigmine overall is generally accepted if amifampridine is not accessible, though its use is not supported by high-quality data.

III. Immunoglobulin is often used in patients specifically for refractory weakness, which may or may not be associated with the underlying cancer in paraneoplastic LEMS. Alternative immunotherapies used include prednisone, azathioprine, plasma exchange, mycophenolate, rituximab.

IV. In trials LMS-002, LMS-003, and DAPPER, subjects were confirmed of diagnosis of LEMS by nerve conduction findings OR positive anti-P/Q type voltage-gated calcium channel antibody test.
   - The clinical presentation of LEMS that of slowly progressive, symmetric and proximal weakness, among other clinical symptoms, indicates a need of specific diagnosis by an experienced specialist.

V. In LMS-002 or LMS-003 (Firdapse), subjects without any prior history of systemic treatment for LEMS, a QMG score of $\geq$ 5 was required.

VI. Trial patients were required to meet inclusion criteria, not limited to, the following (LMS-002, LMS-003):
- No history of other or current respiratory disease and receiving amifampridine.
- Normal swallowing function.
- Completion of cancer treatment at least three months prior to initiation of therapy.

VII. Trial subjects were excluded if the any of the following criteria were met (LMS-002, LMS-003):
- History of epilepsy of seizure.
- Concurrent use of dalfampridine or any form of 3,4-diaminopyridine.
- A forced vital capacity at <1500 mL.
- Use of IVIG within 90 days; use of guanidine within seven days; or use of rituximab within 12 months prior.
- Use of medications that lower seizure threshold or inhibit neuromuscular function.

VIII. Use of amifampridine (Ruzurgi) in the pediatric population is supported by 24 submitted cases and reviewed by the FDA. Additionally, autoimmune LEMS was largely represented in most subjects among all studies. This renders the collected data particularly applicable to the pediatric population as autoimmune LEMS predominates in this population.

IX. The long-term efficacy and safety of amifampridine (Firdapse) was not thoroughly assessed in LMS-002 and LMS-003. Due to the small size of the study population and short duration of exposure and observation, it was likely adverse effects or toxicities resulting from long-term exposure were yet to be identified. Thirty-five adverse events have been reported to the FDA Adverse Event Reporting System since August of 2013. Amifampridine (Firdapse) received FDA approval in November of 2018. Twenty-one events have been reported since FDA-approval as of July 2019.

X. Safety and efficacy of amifampridine (Ruzurgi) is supported by a history of data collected from 247 patients using amifampridine through expanded access, compassionate use program through the FDA, with an average use of five years, range up to 27 years of use. A total of 630 patients have received 3,4-DAP (Ruzurgi) through 230 INDs prior to FDA approval.

XI. There is a lack of strong scientific evidence to support the safety and efficacy for an increased dosing frequency or doses above the recommended. Trials were too small to indicate a dose-related trend of improvement or indicate a variation in effectiveness among subgroup populations.

Investigational or Not Medically Necessary Uses

I. Diagnosis of LEMS is largely based on clinical assessment and rule-out of other symptomatically similar disease. The following disease states have a similar presentation or relatedness to LEMS, however, randomized controlled trials to support the efficacy and safety of amifampridine (Firdapse, Ruzurgi) have yet to be completed.
   A. Inflammatory muscle disease

B. Limb-girdle muscular dystrophy
C. Myasthenia gravis
D. Congenital myasthenic syndrome
E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

References

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2. Ruzurgi [prescribing information]. Plainsboro, NJ: Jacobson Pharmaceutical Company; May 2019.
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Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	July 2019
Last Reviewed	July 2019

Action and Summary of Changes	Date
Addition of Ruzurgi to policy	July 2019