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New Drug Evaluation: amifampridine tablets, oral

Date of Review: November 2019
Generic Name: amifampridine phosphate
amifampridine

End Date of Literature Search: 07/24/2019
Brand Name (Manufacturer): Firdapse® (Catalyst Pharmaceuticals, Inc)
Ruzurgi® (Jacobus Pharmaceutical Company, Inc)
Dossier Received: Firdapse® (yes); Ruzurgi® (no)

Research Questions:

1. What is the efficacy or effectiveness of amifampridine in the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) compared to placebo or other pharmacotherapy?
2. Is amifampridine safe for the treatment of LEMS?
3. Are there subgroups of patients (i.e. those based on age, gender, ethnicity, disease severity, or comorbidities) that are associated with more effectiveness or harm while treated with amifampridine?

Conclusions:

- In two trials with 64 LEMS patients, there was low quality evidence that amifampridine was associated with a statistically significant least squares mean difference (LSMD) in quantitative myasthenia gravis (QMG) score at 4 days, but not after 14 days of treatment [(LSMD of -6.54; 95% CI -9.78 to -3.29) and (LSMD of -1.7; 95% CI -3.4 to 0), respectively].[1,2] The QMG scale ranges from 0-39, with higher scores indicating greater impairment and clinically meaningful change has been suggested as a decrease in 2.6 points or more.[1,2]
- There was low quality evidence that amifampridine demonstrates a statistically significant improvement in the subject global impression (SGI) score in LEMS patients after treatment versus placebo at 14 days (LSMD of 1.8; 95% CI 0.7 to 3.0) and also at 4 days (LSMD 2.95; 95% CI 1.53 to 4.38).[1,2] It remains unknown if a 2-3 point difference in the SGI score represents a clinically relevant or noticeable to the patient since this outcome has not been validated in other clinical trials.
- There was low quality evidence that a greater percentage of placebo patients experienced decreased mobility at day 4 based on the Triple Timed Up and Go test (3TUG) measurement compared to patients in the continuous amifampridine group (72.2% vs. 0%, respectively; $p<0.0001$).[3]
- There is no data to compare different amifampridine formulations, and it is unclear if the observed changes in QMG score, SGI score, or the 3TUG test correlate to actual changes in disease progression, functional status, or quality of life.
- Amifampridine use is associated with seizure risk and other adverse reactions such as dysesthesia, upper respiratory tract infection, abdominal pain, dyspepsia, nausea, diarrhea, headache, elevated liver enzymes, back pain, muscle spasms, and hypertension.[4]
- There is insufficient evidence to evaluate the safety and efficacy of amifampridine in any subgroups of patients with LEMS.
- There is insufficient evidence to evaluate the long-term safety and efficacy of amifampridine in LEMS treatment beyond 14 days.

Author: Victor Rojo, Pharm.D. Candidate, 2020

Recommendations:

- Create a new PDL class for LEMS agents.
- Implement prior authorization criteria for amifampridine **(Appendix 2).**
- Review costs in executive session.

Background:

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular disorder characterized by deficient nerve impulse transmission and progressively debilitating muscle weakness.[5] In LEMS patients, it is believed that antibodies to the voltage-gated calcium channels (VGCCs) prevent depolarization of the presynaptic neuron and subsequent release of the neurotransmitter acetylcholine (ACh) which is normally responsible for stimulation of myocyte activity.[6,7] With VGCC blockade, calcium ions are unable to influx the presynaptic cell which results in neuromuscular transmission impairment.[6] The $alpha_1$ subunit of a VGCC provides several binding sites, including the common P/Q-type which are believed to be the primary target for autoantibodies in LEMS.[7]

Patients with LEMS typically present with fatigue and strength deficiency notably in the proximal leg muscles.[5] This weakness impairs mobility and may progress to other muscles of the hands, feet, and eventually the head.[5] As more cranial muscles become affected, there is increased evidence of chewing or swallowing difficulties, speech impairment, ptosis, and visual disruption.[8-11] Other common symptoms of autonomic neuropathy in LEMS include hypohidrosis, xerostomia, and dry eyes.[9,10] Though symmetrical muscle involvement is the predominant presentation in LEMS, unilateral, regional weakness has been documented in patients as well.[11] Approximately half of all LEMS cases are paraneoplastic manifestations and caused by a small cell lung carcinoma (SCLC).[8,12,13] VGCCs are expressed on the surface of SCLC cells and it has been hypothesized that antibodies produced to fight SCLC cells cross-react with VGCCs at the neuromuscular junction.[8,12,13] Treatment of the underlying malignancy has been shown to significantly improve symptoms in patients with concurrent LEMS and SCLC.[8] Patients with LEMS but no evidence of SCLS are categorized as non-paraneoplastic autoimmune LEMS or non-tumor LEMS (NT-LEMS).[8,12,13] In the absence of cancer, NT-LEMS patients do not appear to have a shortened life span, but the disease may impact quality of life.[8] The prevalence of LEMS is estimated to be roughly 3 persons per 1,000,000.[13] Claims data from April 2018 through March 2019 revealed 8 unique patients diagnosed with LEMS in Oregon's Fee-for-Service (FFS) and Coordinated Care Organizations (CCOs).

There is no known cure for LEMS but a variety of agents have been utilized to provide symptomatic treatment. Agents that increase neurotransmitter release at the neuromuscular junction have been shown to assist with LEMS-related muscular dysfunction.[14] Until 2018, guanidine was the only agent FDA-approved for symptomatic relief of muscle weakness and fatigue in patients with LEMS.[14-16] However, guanidine use has been limited due to serious adverse effects including bone marrow depression and renal failure.[14-16] Cholinesterase inhibitors such as pyridostigmine have been used as monotherapy to treat LEMS symptoms with modest success.[15,17] Pyridostigmine used in combination with low doses of guanidine was determined to be effective and safer than guanidine monotherapy, although, pyridostigmine has also demonstrated dose-dependent adverse effects such as nausea, abdominal cramping, and diarrhea.[18] 4-aminopyridine (dalfampridine) had been tested in the past, but its usefulness was limited by the potential to cause seizures and other central nervous system adverse effects.[14,19]

Immune system modulators have also been utilized to treat LEMS symptoms. Intravenous immunoglobulin (IVIG) at variable doses and frequencies may improve limb strength.[20,21] Immunosuppressive treatments such as mycophenolate, cyclosporine, and rituximab have been used, however, delayed response to treatment and significant adverse effects limit their widespread use.[12,14,16,19,22,23] Azathioprine combined with prednisone has demonstrated some symptomatic improvement in LEMS patients, but with a recommended dose taper of prednisone to reduce toxicity.[12,22] In severe or refractory muscle weakness due to LEMS,

immunomodulating therapy has been used with mixed benefit.[12,14 21] Some studies have suggested positive peripheral muscle outcomes in LEMS treatment with plasmapheresis, though a minimum of five exchanges may be necessitated.[24]

Amifampridine (3,4-DAP or 3,4-Diaminopyridine) has been a rational LEMS treatment option for many years.[14,19] Amifampridine is thought to improve ACh release from the presynaptic neuron by blocking potassium channels and prolonging depolarization of the nerve terminal followed by an increase in calcium influx and ACh efflux.[14] Until recently amifampridine never had formal FDA approval, although the drug had been reported to be safe and effective in human studies.[19] Jacobus Pharmaceutical Co, Inc (JPC) had historically made amifampridine available to patients in the United States for free through a compassionate use program.

The goal of LEMS treatment is to provide symptomatic relief and improve quality of life. A variety of assessments have been used in clinical trials to assess LEMS therapy outcomes. The QMG is a 39 point assessment scale in which the physician rates a patient's muscle strength on a scale of 0 (no weakness) to 3 (severe weakness) in 13 different parameters such as ability to swallow, facial muscle function, hand-grip strength, and vital capacity.[1,25] One study defined a minimal clinically important difference (MCID) in QMG to be a change of 2.6 points when used as a primary outcome measure.[25] The subject global impression (SGI) score is a patient-rated scale of 1 (terrible) to 7 (delighted) that reflects the patient's global impression of how they feel symptoms are being managed with treatment.[1,2] No clinically important difference was identified for SGI. Other scales to evaluate patient functional improvement and severity of illness have been reported in the literature such as the Clinical Global Impressions (CGI) scale.[26] The CGI-I is a 7-point scale designed to assess improvement in generalized patient function which ranges from 1 (very much improved) to 7 (very much worse).[26] The CGI-S is also a 7-point scale but is focused on assessment of patient mental health and scored from 1 (normal, not at all ill) to 7 (among the patients who are most ill).[26] There has been no published literature to support a MCID value for a CGI score in LEMS patient assessment. Other outcomes used in studies to assess the clinical benefit of LEMS therapies have included timed walk tests.[27,28] In the Timed Up-and-Go (TUG) test, patients are timed how long it takes to arise from a seated position, walk 3 meters, and then return to a seated position.[29] The TUG test has been used as an assessment of basic functional mobility in movement disorders of the frail elderly with a suggested MCID of 4 seconds[29] Some trials have used modified versions of the TUG test such as the triple timed up-and-go test (3TUG) which has not been validated as a clinical outcome measure in LEMS patients.[3]

Systematic Reviews:

The Cochrane Collaboration performed a systematic review for the medical treatment of LEMS.[30] The review identified 5 randomized, double-blind, placebo-controlled trials of adult patients with LEMS (N=66).[30] None of the included studies contained formulations of agents FDA-approved for use in LEMS. Participants were treated with amifampridine (3,4-Diaminopyridine) for up to 8 days in 4 of the studies and with IVIg for 8 weeks in one study.[30] At the time of the review, amifampridine was frequently used in Europe for symptomatic LEMS treatment but none of the .[30] The primary outcome was change in muscle strength as measured by the (QMG score or limb muscle strength measured by myometry.[30] The studies were rated as low risk of bias in the major domains, however, allocation concealment had an unclear risk of bias in all but one study.[30]

Four of the studies used a muscle strength scale as a primary or secondary outcome measure and reported significant improvement in muscle strength score or myometric limb measurement after treatment.[30] The four amifampridine studies were not able to be combined for meta-analysis because the primary outcomes reported an alternate muscle strength score from the QMG and lack of details in the scoring systems prevented calculation of an equivalent QMG score.[30] However, there was moderate to high quality evidence from two of the small studies that demonstrated the QMG muscle score assessed between 3 and 8 days was likely to decrease (improve) by a mean of -2.44 points (95% CI -3.65 to -1.22) after treatment with amifampridine compared to placebo.[30] The authors of the IVIg study reported IVIg patients had significant improvement in limb strength as measured by myometry compared to placebo, however, no

QMG score or validated muscle strength assessment tool was used to measure treatment effect.[30] Due to the relatively short study durations, small sample size, and differences between primary outcome measures, there was insufficient data to quantify the true treatment effect of amifampridine (3,4-DAP) and IVIg in LEMS patients.

NEW DRUG EVALUATION: Amifampridine phosphate (Firdapse ™); Amifampridine (Ruzurgi ™)

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Amifampridine is an orally administered potassium channel blocker indicated for the treatment of LEMS patients. Amifampridine is proposed to act on presynaptic nerve membranes to cause an influx of calcium ions and a corresponding acetylcholine efflux from the presynaptic neuron to improve muscle activity.[27,28] Firdapse™ (amifampridine phosphate) is FDA approved for the treatment of LEMS symptoms in adults and Ruzurgi™ (amifampridine) is approved in patients aged 6 to less than 17.[27,28]

Firdapse™
The safety and efficacy of amifampridine phosphate was studied in two phase 3, double-blind, randomized, placebo-controlled discontinuation studies (LMS-002 and LMS-003).[27] LMS-002 included adult patients (n=38) with a mean age of 52, a confirmed diagnosis of LEMS, and normal swallowing function.[27] Patients without a history of symptomatic LEMS treatment were required to have a baseline QMG score of at least 5 (minimal symptoms).[27] Patients were also required to have at least 80% forced vital capacity (FVC) of predicted respiratory function or at least 60% for amifampridine-naive patients.[27] Full inclusion and exclusion criteria may be found in the evidence table (**Table 3**). Fifty-four patients initially entered a 3-month open-label titration period to allow investigator to optimize therapeutic response to amifampridine.[27] After roughly 30% of subjects withdrew due to adverse events, lack of efficacy, or personal reasons, patients were then allocated to either 7 days of continued amifampridine therapy or gradual taper to placebo followed by a 7-day maintenance period in a double blinded discontinuation phase. Primary outcome assessments were performed at the conclusion of the two-week period.[27] The primary study endpoints were changes in QMG and SGI scores from baseline to day 14.[27] Secondary endpoints were the CGI-I score on day 14 and the change in Timed 25-Foot Walk (T25FW) test speed from baseline.[1] A 20% change in average 3TUG time was evaluated as an exploratory endpoint. Forty of the 54 patients (74%) entered a 2-year optional open-label, safety assessment of amifampridine treatment.[1]

At 14 days, the mean change in QMG score from baseline was 0.4 for amifampridine and 2.2 for placebo (higher scores indicate worse symptoms) with a difference in least squares means of -1.8 (95% CI -3.4 to 0).[1,27] QMG score changes were not statistically significant based on the reported confidence interval. In contrast, there was a statistically significant change from baseline in SGI score for amifampridine-treated patients versus placebo (-0.8 and -2.6, respectively, lower scores indicate worse outcomes) at 14 days with a LSMD of 1.8 (95% CI 0.7 to 3.0).[1,27] The change from baseline in the secondary endpoint of CGI-I was reported to be lower in amifampridine-treated patients versus placebo (3.6 vs 4.7, respectively – higher scores worse) at day 14 with a statistically significant LSMD of -1.1 (95%CI -2.1 to -0.1). The clinical significance of a 1.8-point change in the SGI score or a 1.1-point change on the CGI-I scale is unknown. The LSMD between amifampridine and placebo in the T25FW test was not statistically significant on Day 14.[1,27]

LMS-003 was a 4-day study of 26 adult patients who were already on amifampridine phosphate through an Expanded Access Program (EAP). Participants were titrated to optimal dose and frequency of amifampridine for at least 1 week before 1:1 randomization to amifampridine phosphate or placebo.[2,27] Unlike LMS-002, this trial did not exclude patients with current use of dalfampridine orguanidine.[2,27] Full inclusion and exclusion criteria may be found in **Table 3.** Blinded study medication was given on days 1 through 3.[2,27] On day 4, doses were administered in clinic where assessments were performed 45 minutes after the last treatment dose.[2,27] Upon study completion, patients were eligible to return to the EAP with open-label amifampridine.[2,27] Primary endpoints were change in QMG and SGI scores from baseline to day 4, while the secondary endpoint was the CGI-I score on day 4.[2,27]

At 4 days, the authors reported a statistically significant change from baseline in the QMG score with the amifampridine group compared to placebo (0.0 vs. 6.54; LSMD -6.54 [95% CI, -9.78 to -3.29]).[2,27] There was also a statistically significant difference in SGI scores in the amifampridine group versus placebo (-0.64 vs. -3.9; LSMD 2.95 [95% CI 1.53 to 4.38]).[2,27] For the secondary outcome of CGI-I score change, there was a statistically significant difference in the amifampridine group versus placebo (3.8 vs. 5.5, p=0.002; 95% CI not reported).[2,27] While the author's did report a statistically significant difference in the 3TUG evaluation, the FDA reviewers had concerns that the outcome was not corrected for multiplicity and could represent a chance finding. Therefore, the manufacturer did not include the 3TUG outcome in the labeling and details will not be presented.

Ruzurgi™

A different formulation of amifampridine was approved by the FDA for the treatment of LEMS in patients aged 6 to less than 17 years.[28] Amifampridine safety and efficacy was studied in a double-blind placebo-controlled discontinuation trial, 3,4-DAP Product Efficacy Research (DAPPER). [3,28] Primary efficacy was assessed through percent change in the Triple Timed Up and Go test (3TUG) and the main secondary endpoint was measured via a LEMS Weakness Self-Assessment Scale (W-SAS).[3,28] The 3TUG was a sponsor modified version of the TUG where patients completed 3 continuous TUG test repetitions instead of one and the 3 lap times were averaged.[3] The investigators claimed this variation of the TUG was necessary to accommodate the neuromuscular fatigue that may affect patients with LEM to different degrees.[3] The W-SAS was a sponsor-developed 7-level categorical scale to demonstrate participant-perceived changes in strength with scores that range from -3 ("much, much weaker") to +3 ("much, much stronger").[3,28] The study was small (n=32), with a blinded treatment period of 4 days, and included only patients with a positive response to continuous 3,4-DAP therapy. [3,28] Specific inclusion and exclusion criteria are listed in **Table 3**.

Fifty-two patients underwent a 4-week outpatient screening and admission period to assess initial eligibility.[3,28] Thirty-two of the patients with a sufficient response to the 3TUG test were randomly assigned to either continue the 3,4-DAP active treatment or were allocated to a taper-to-placebo group.[3,28] Over the next 3.5 days, the amifampridine dose was slowly decreased in the taper-to-placebo group until they were without active treatment for a total of 16 hours.[3,28] The 3TUG outcome measure was the proportion of patients with a >30% deterioration in time. W-SAS scores were also assessed at that time.[3,28]

In LEMS patients, a greater percentage of patients in the taper-to-placebo group deteriorated in the 3TUG test compared to patients in the continuous amifampridine group (72.2% vs 0%, respectively; p<0.0001).[3,28] In addition, the investigators reported a statistically significant mean difference in the W-SAS score for the taper-to-placebo group compared to the continuous amifampridine group (-2.4 vs -0.2 respectively; p<0.0001, lower scores worse).[3,28] The clinical significance of a 2.2-point difference in an unvalidated global assessment tool is unclear.

These trials involved a small number of subjects with very short treatment durations. The long run-in period prior to randomization selected only patients with a clear response to amifampridine which, in a discontinuation study design, may have led to an overestimation of treatment benefit. Since the study population had already been stable on doses of amifampridine, which has a short half-life, there was increased risk for unblinding of patients and investigators during the withdrawal period. The majority of assessment tools used in the amifampridine studies were unvalidated. Certain tools such as the SGI and CGI-I were highly

subjective measures of patient symptoms and function with no clear MCID for clinical interpretation. Mean baseline values of the 3TUG test and the complete data for the T25FW were not reported which made it difficult to assess the two most clinically relevant endpoints of patient ambulatory ability.

Clinical Safety:

The most common adverse effects of amifampridine seen in more than 10% of patients are included in **Table 1**.[27,28] No serious adverse effects were reported in the controlled trials.[1-3] The FDA required the manufacturer to add seizures as a warning/precaution on the label based on animal toxicology studies and clinical findings from structurally related compounds, such as 4-aminopyridine.[27,28] The maximum daily dose of Firdapse® is 80 mg and Ruzurgi® is restricted to 100 mg daily as doses of amifampridine above this threshold have been associated with an increase seizure risk.[27,28] Suggested dosing for amifampridine may be found in **Appendix 1**.

Sufficient data for amifampridine risk assessment does not exist in the following subpopulations: pregnancy, lactation, children under 6 years old, and adults aged 65 and older.[27,28] Amifampridine is metabolized by N-acetyltransferase 2, so poor metabolizers or patients with hepatic impairment are at increased risk of drug exposure and are advised to take the lowest recommended starting dose.[27,28] Amifampridine and its inactive metabolite, 3-N-acetyl amifampridine, are both renally eliminated and should be adjusted to the lowest recommended starting dose in patients with renal impairment.[27,28] All subgroups should be monitored closely for intolerability or negative clinical effects.[27,28]

Table 1. Adverse Reactions in >10% of LEMS Patients Newly Treated with Amifampridine*[27,28]

Adverse Reaction	Amifampridine (n=143 combined)
Dysesthesia (paresthesia, dysesthesia, oral dysesthesia)	62-69%
Upper respiratory tract infection	33%
Abdominal pain	14-25%
Dyspepsia	17%
Diarrhea	14%
Headache	14%
Elevated liver enzymes	14%
Nausea	10-14%
Back pain	8-14%
Hypertension	12%
Muscle spasms	6-12%
Dizziness	10-12%

*=placebo rates not available

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Improvement in muscle strength
2) Improvement in ambulation
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Quantitative Myasthenia Gravis (QMG) score
2) Subject Global Impression (SGI)
3) Triple Timed Up and Go test (3TUG)

Table 2. Pharmacology and Pharmacokinetic Properties.[27,28]

Parameter	
Mechanism of Action	Produces calcium influx into, and subsequent acetylcholine release from, presynaptic nerve membrane via potassium channel blockade
Oral Bioavailability	Rapidly absorbed, and peak plasma concentration (C_{max}) were reached 30 to 90 minutes after ingestion in the fasting state; roughly ~41%-52% decrease in C_{max} and ~9%-23% decrease in AUC0-∞, and delay in T_{max} by ~1 hour when amifampridine was administered with high fat meal compared to fasted state (Ruzurgi)
Distribution and Protein Binding	467 L (Firdapse); 357 – 1383 L (Ruzurgi); 25.3% protein binding (Ruzurgi)
Elimination	93-100% (Firdapse); >65% (Ruzurgi); Eliminated as unchanged amifampridine and 3-N-acetyl amifampridine
Half-Life	1.8-2.5 hours (Firdapse), 3.6-4.2 hours (Ruzurgi)
Metabolism	Via N-acetyltransferase to 3-N-acetylamifampridine (inactive metabolite); rate and extent of metabolism of amifampridine is affected by polymorphism in the NAT2

Abbreviations: L = liters; NAT2 = N-acetyltransferase gene 2

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Oh et al.[1,27] Phase 3 MC RCT, DB, PC, withdrawal study 91-day open-label run in period followed by 14-day randomized DB treatment	1. Amifampridine phosphate (20-80 mg/day) 2. Taper to Placebo Dosed orally tid-qid x14 days	Demographics: - Mean Age: 52 (range: 21-88) - Female: 61% - White: 90% - PEF ≥100%: 55% - Positive VGCC antibody: 92% - Hx Cancer: 16% - Treatment-experienced: 26% - Baseline QMG, Part 2 Day 1: 6 +/- 4 Key Inclusion Criteria: - Age ≥ 18 - Treatment-naïve QMG score ≥5 - FVC ≥80% predicted for treatment-experienced; ≥60% for treatment-naive - Normal swallowing function - Completion of anti-cancer treatment ≥3 months prior to screening Key Exclusion Criteria: - Known seizure hx - Active brain metastases - Serious electrocardiogram abnormalities - concurrent use of dalfampridine or any form of 3,4-DAP - IVIg or plasmapheresis in previous 90 days, guanidine within previous 7 days, or rituximab within previous year	ITT: 1. 16 2. 22 Attrition: 1. 0 2. 2 (9%)	Primary Endpoints: 1. LSM CFB in QMG Amifampridine: 0.4 Placebo: 2.2 MD: -1.8* (95% CI, -3.4 to 0.0) *= reported -1.7 p = 0.0452 2. LSM CFB in SGI Amifampridine: -0.8 Placebo: -2.6 MD: 1.8 (95% CI, 0.7 to 3.0) p = 0.0028 Secondary Endpoint: LSM CFB CGI-I Amifampridine: 3.6 Placebo: 4.7 MD: -1.1 (95% CI -2.1 to -0.1) p=0.0267 CFB in T25FW in ft/min Amifampridine: -1.16 Placebo: -9.67 MD: -8.51 (95% CI, -26.77 to 43.79) p-value = 0.6274 All outcomes evaluated at Day 14	NA for all	SAEs: 1. 0 2. 0 Discontinuation due to Adverse Events: 1. 0 2. 2 TEAEs During Open Label Run-in: (N = 53) -Oral paresthesia: 21 (39.6%) -Digital paresthesia: 18 (34%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomization and allocation concealment methods not documented. Performance Bias: Unclear. Subjects reportedly blinded, but methods undefined. Possibility of unblinding due to dose withdrawal study design. Detection Bias: Unclear. Assessors reportedly blinded, but methods undefined; blinding potentially broken due to known adverse effects such as dysesthesia Attrition Bias: Low. <10% overall attrition and between-group dropout rate. Reporting Bias: High. Not all outcome data reported in PP and ITT analyses. Published trial data is inconsistent with FDA analysis. QMG outcome reported to be statistically significantly different in favor of treatment but CI values are contradictory. Other Bias: Unclear. Study was funded by manufacturer. Many major authors served as consultants for or received research funding from manufacturer. **Applicability**: Patient: Adult patients only; mostly white. 3-month run-in period where roughly 30% patients withdrew mostly for adverse effects; extensive exclusion criteria limits applicability notably patients with respiratory or cardiac dysfunction. Intervention: Efficacy evaluation period over 14 days. Study dosing consistent with clinical practice dosing Comparator: Taper to placebo comparator. Study only enrolled subjects known to respond to amifampridine. Guanidine may have been a more appropriate comparator. Outcomes: QMG, SGI, and CGI-I were short-term subjective outcome measures with potential for inconsistent interpretation. T25FW not validated as outcome measure for LEMS patients and subject to variability. Setting: 18 sites within the United States, European Union, and Russian Federation

2. Shieh et al.[2, 27] Phase 3 RCT, DB, PC, withdrawal study	1. Amifampridine phosphate (30-80 mg/day) 2. Taper to Placebo Dosed orally tid-qid x4 days	Demographics: - Mean Age: 54 (range: 31-75) - Female: 62% - White: 81% - Mean BMI: 29.4 (range: 20.6-40.1) kg/m2 - PEF ≥100%: 92% - Positive VGCC antibody: 88% - Cancer: 23% - Daily amifampridine dose at study entry: 61.5 mg ± 18.60 - Baseline QMG: 1. 7.8 +/- 4.2 2. 8.5 +/- 5.4 - Baseline SGI: 1. 6.1 +/- 0.9 2. 5.8 +/- 0.9 Key Inclusion Criteria: - Age ≥18 - Diagnosis of LEMS - Cancer patients required to have completed anticancer treatment ≥3 months before study entry Key Exclusion Criteria: - Clinically significant prolonged interval on ECG within the previous 12 months - Hx of seizure disorder - Active brain metastases - Inability to ambulate - Pregnant or lactating females - Inability to d/c immunomodulatory treatment within 3 weeks before study entry	ITT: 1. 13 2. 13 Attrition: 1. 0 2. 0	Primary Endpoints: 1. CFB in QMG Amifampridine: 0.7 Placebo: 7.1 RR: -6.54 (95% CI, -9.78 to -3.29) p = 0.0004 2. CFB in SGI Amifampridine: -0.3 Placebo: -2.9 RR: 2.95 (95% CI, 1.53 to 4.38) p = 0.0003	NA for all	SAEs: 1. 0 2. 0 TEAEs During Open Label Run-in: (N = 53; FDA included both Oh and Shieh studies) -Paresthesia (included paresthesia, oral paresthesia and oral hypoesthesia) 26 (49%) -URTI 21 (40%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomization and allocation concealment undefined. Performance Bias: Unclear. Subjects blinded, but blinding methods undefined. Detection Bias: Unclear. Assessors blinded, but blinding methods undefined. Attrition Bias: Low. No missing data. Reporting Bias: High. 3TUG time was pre-specified as an exploratory outcome, but data not reported in the analysis. Many outcomes reported in detail but were not pre-specified in methods (forced vital capacity, head lift 45°). Other Bias: Unclear. Conflicts of interest not reported. Study author has served as consultant for manufacturer. **Applicability**: Patient: Adult patients only; all participants selected from expanded access program Intervention: Study dosing consistent with clinical practice dosing Comparator: Taper to placebo comparator; Study only enrolled subjects known to respond to amifampridine. Guanidine may have been a more appropriate comparator. Outcomes: Efficacy endpoints were subjective; QMG and SGI scores at 4-days with no long term data available Setting: 3 centers in the United States

3.DAPPER [3,28] Phase 2, multicenter, RCT, PC, DB, withdrawal study 4-week screening followed by 1-week assessment	1. Continuous 3,4-DAP 2. Taper to placebo Duration: 7 days tx; 4-week follow-up 3,4-DAP doses: -30 mg/day in 3 divided doses up to 100 mg/day max	Demographics: Median age: -3,4-DAP group: 49 -taper to PBO: 63.5 Female: 66% White: 91% Median age at time of LEMS diagnosis: -3,4-DAP group: 46 -taper to PBO: 59.5 Key Inclusion Criteria: - ≥18 yo; ambulatory - Established LEMS dx - Continuous 3,4-DAP use ≥3 months; ≥3 doses/day of ≥10 mg 3,4-DAP - First morning dose positive response to 3,4-DAP - ≥3 months stable on LEMS-related therapies Key Exclusion Criteria: - Last MAB treatment < 6 months prior - Clinically significant or poorly controlled co-morbidity -Respiratory failure requiring intubation while on 3,4-DAP - Investigational drug use besides 3,4-DAP in last 30 days before study - Pregnant/lactating - Current use of other aminopyridines (e.g., 4-AP) or guanidine - No sufficient baseline response to 3,4-DAP at baseline to detect a ≥30% decline during 3,4-DAP withdrawal	ITT: 1. 14 2. 18 Attrition: 1. 0 2. 0	Primary Endpoint: >30% deterioration in final 3TUG test performance upon withdrawal of 3,4-DAP 1. 0/0% 2. 13/ 72.2% P<0.0001 No CI reported Secondary Endpoint: Subject Self-Assessment of LEMS-Related Weakness (W-SAS) Final Score: "Somewhat weaker", Much weaker" or "Much much weaker": 1. 3 (21%) 2. 17 (94%) P<0.0001	72.2% /2 73%/2	SAEs: 1. 0 2. 1 TEAEs from Expanded Access Dataset, N = 159) -paresthesia 56 (36.5%) -fall 21 (13.2%) -diarrhea 20 (12.6%) -pneumonia 16 (10.1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Participants randomized centrally 1:1 but randomization and allocation concealment methods undefined; Sponsor determined if individual eligibility was met based on 3TUG pre-trial assessment Performance Bias: Unclear. Identical tablets and centralized packaging used to ensure blinding of all subjects and investigators; only responders to active agent were enrolled and randomized Detection Bias: Unclear. Central reader blinded to treatment videotaped and scored the 3TUG tests. FDA noted several data discrepancies which required re-analysis. Attrition Bias: Low. All patients completed study. ITT population included all patients randomized, as well as patients who were replaced due to withdrawal of consent after randomization but prior to admission. Reporting Bias: Unclear. Baseline 3TUG scores unavailable for comparison. Other Bias: Unclear.; Jacobus Pharmaceutical Company, Inc, sponsored the research; lead authors were consultants for manufacturer **Applicability**: Patient: All patients studied were adults so efficacy in children is unclear. FDA approval was based on efficacy and safety data from expanded access programs. Intervention: Mean TDD at baseline was roughly 75 mg. Unable to evaluate dose response with respect to clinical efficacy especially in pediatric population based on this study Comparator: Taper to placebo. Guanidine may have been a more appropriate comparator for adult population. Outcomes: 3TUG performance after only 1-week, long term effects are unclear Setting: 7 centers across the United States

Abbreviations [alphabetical order]: 3TUG = triple timed up and go.; ARR = absolute risk reduction; BMI = body mass index; CFB = change from baseline; CGI-I: Clinical Global Impression-Improvement Score; CI = confidence interval; DB = double blind; ECG = electrocardiogram; FVC = forced vital capacity; Hx = history; ITT = intention to treat; LEMS = Lambert-Eaton Myasthenic Syndrome; LSM = least squares mean; MAB = monoclonal antibody; MC = multicenter; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PBO = placebo; PC = placebo controlled; PEF = post-exercise facilitation; PP = per protocol; QID = four times daily; QMG = quantitative myasthenia gravis score; RCT = randomized

controlled trial; SAE = serious adverse event; SGI = subject global impression; T25FW = timed 25-foot walk test; TDD = total daily dose; TID = three times daily; URTI = upper respiratory tract infection; VGCC = voltage-gated calcium channel.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RUZURGI safely and effectively. See full prescribing information for RUZURGI.

RUZURGI (amifampridine) tablets, for oral use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

RUZURGI is a potassiumchannel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age. (1)

DOSAGE AND ADMINISTRATION

- Patients 6 to less than 17 years of age weighing 45 kg or more:
  - Initial dosage is 15 mg to 30 mg daily, in divided doses
  - Increase daily in 5 mg to 10 mg increments, divided in up to 5 doses daily
  - Maximum single dose is 30 mg; maximum daily dosage is 100 mg (2.1)
- Patients 6 to less than 17 years of age weighing less than 45 kg:
  - Initial dosage is 7.5 mg to 15 mg daily, in divided doses
  - Increase daily in 2.5 mg to 5 mg increments, divided in up to 5 doses daily
  - Maximum single dose is 15 mg; maximum daily dosage is 50 mg (2.1)
- When patients require a dosage in less than 5 mg increments, have difficulty swallowing, or require feeding tubes, a 1 mg/mL suspension can be prepared. (2.2)
- For patients with renal or hepatic impairment or who are known N-acetyltransferase 2 poor metabolizers, use the lowest recommended initial dosage. (2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, functionally scored (3)

CONTRAINDICATIONS

- History of seizures (4)
- Hypersensitivity to amifampridine or other aminopyridine (4)

WARNINGS AND PRECAUTIONS

- RUZURGI can cause seizures. Consider discontinuation or dose-reduction of RUZURGI in patients who have a seizure while on treatment. (5.1)
- Hypersensitivity reactions: If a hypersensitivity reaction such as anaphylaxis occurs, RUZURGI should be discontinued and appropriate therapy initiated. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and at least 2% greater than placebo) are paresthesia/dysesthesia, abdominal pain, dyspepsia, dizziness, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jacobus at 609-921-7447 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Drugs that lower seizure threshold: The concomitant use of RUZURGI and drugs that lower seizure threshold may lead to an increased risk of seizures. (7.1)
- Drugs with cholinergic effects: The concomitant use of RUZURGI and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of RUZURGI and of those drugs, and increase the risk of adverse reactions. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FIRDAPSE® safely and effectively. See full prescribing information for FIRDAPSE®.

FIRDAPSE® (amifampridine) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

FIRDAPSE is a potassiumchannel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 15 mg to 30 mg daily taken orally in divided doses (3 to 4 times daily). (2.1)
  - Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment, and in known N-acetyltransferase 2 (NAT2) poor metabolizers (2.2, 2.3, 2.4)
- Dosage can be increased by 5 mg daily every 3 to 4 days. (2.1)
- Dosage is not to exceed a maximum of 80 mg daily. (2.1)
- The maximum single dose is 20 mg. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 10 mg, functionally scored. (3)

----------CONTRAINDICATIONS----------

FIRDAPSE is contraindicated in patients with:

- A history of seizures (4)
- Hypersensitivity to amifampridine or another aminopyridine (4)

----------WARNINGS AND PRECAUTIONS----------

- Seizures: FIRDAPSE can cause seizures. Consider discontinuation or dose-reduction of FIRDAPSE in patients who have a seizure while on treatment. (5.1)
- Hypersensitivity reactions: If a hypersensitivity reaction such as anaphylaxis occurs, FIRDAPSE should be discontinued and appropriate therapy initiated. (5.2)

----------ADVERSE REACTIONS----------

The most common (> 10%) adverse reactions are: paresthesia, upper respiratory tract infection, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, and muscle spasms. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Catalyst Pharmaceuticals at 1-844-347-3277 (1-844-FIRDAPSE) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Drugs that lower seizure threshold: The concomitant use of FIRDAPSE and drugs that lower seizure threshold may lead to an increased risk of seizures. (7.1)
- Drugs with cholinergic effects: The concomitant use of FIRDAPSE and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of FIRDAPSE and of those drugs, and increase the risk of adverse reactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Amifampridine

Goal(s):

- Promote safe and effective use of amifampridine in the treatment of LEMS symptoms

Length of Authorization:

- Initial: 14 days
- Renewal: 1 to 3 months

Requires PA:

- Amifampridine

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Maximum Recommended Dose

Formulation	Minimum age (years)	Weight (kg)	Single Dose Maximum	Cumulative Daily Maximum
Ruzurgi®	≥ 6	≤ 45	15 mg	50 mg
		≥ 45	30 mg	100 mg
Firdapse®	≥ 18		20 mg	80 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis for Lambert-Eaton Myasthenic Syndrome (LEMS)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to # 5
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there evidence based on chart notes or claims that the patient has a seizure disorder diagnosis or history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is there evidence based on chart notes or claims that the patient has active brain metastases?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have a documented baseline ECG in the past 12 months demonstrating a QT interval < 450 milliseconds?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the amifampridine dose within the appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient been assessed with a baseline qualitative myasthenia gravis (QMG) exam (score>5), 3TUG walking test, or other validated measure of LEMS patient physical functioning?	**Yes:** Go to #11 Document baseline results.	**No:** Pass to RPh. Deny; medical appropriateness
11. Does the patient have follow-up appointments scheduled during weeks 1 and 2 after the proposed therapy initiation date?	**Yes:** Go to #12 Document appointment dates.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Will the patient and provider comply with all case management interventions and adherence monitoring requirements required by the Oregon Health Authority?	**Yes:** Approve for 2 weeks	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking amifampridine for ≥1 week AND has there been documented improvement from baseline in ambulation or physical functioning as assessed via the 3TUG, QMG score, or other validated LEMS assessment scale?	**Yes:** Document follow-up assessment scores Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the amifampridine dose within appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient experienced any new adverse effects since starting amifampridine therapy (e.g. seizures, arrhythmias)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Does the patient have documented evidence of >90% adherence to amifampridine for the previous approval period?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been on >30 days of continuous amifampridine therapy?	**Yes:** Approve for 3 months	**No:** Approve for 30 days; Renewal consideration will require documentation of tolerance, clinical benefit, and adherence.