AMIFAMPRIDINE PHOSPHATE: AN OVERVIEW

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Abstract- **Amifampridine is used to treat many of the congenital myasthenic syndromes, particularly those with defects in choline acetyltransferase, downstream kinase 7, and those where any kind of defect causes "fast channel" behaviour of the acetylcholine receptor. It is also used to treat symptoms of Lambert–Eaton myasthenic syndrome Amifampridine, or 3,4-diaminopyridine (3,4-DAP), is a quaternary ammonium compound that blocks presynaptic potassium channels, and subsequently prolongs the action potential and increases presynaptic calcium concentrations. LEMS is a rare auto-immune disorder of the neuromuscular junction that is characterized by proximal muscle weakness, depressed tendon reflexes, and posttetanic potentiation in addition to autonomic dysfunction. Amifampridine improves muscle strength and resting compound muscle action potential (CMAP). Amifampridine phosphate is a more stable salt that serves as an active ingredient of EMA-approved Firdapse, which was previously marketed as Zenas. . Amifampridine is the nonimmune treatment options for LEMS. In phase III clinical trials of adult patients with LEMS, treatment of amifampridine significantly improved symptoms of LEMS compared to placebo with good tolerance. Amifampridine is indicated for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients.**

Keywords: **Amifampridine Phosphate (FIRDAPSE), Lambert–Eaton myasthenic syndrome(LEMS),Blocking potassium channel efflux, Neuro Muscular Junctions (NMJs).**

Objective: The purpose of this article is to review the literature for **3,4-diaminopyridine (3,4-DAP) amifampridine** for the treatment of Lambert-Eaton myasthenic syndrome **(LEMS).**

INTRODUCTION:

Amifampridine (am" i fam' pri deen) is a diaminopyridine that acts on peripheral potassium channels and is used to treat the Lambert-Eaton myasthenic syndrome, a rare form of myasthenia suspected to be autoimmune in nature. Amifampridine is used as a drug, Amifampridine is used as a drug, predominantly in the treatment of a number of rare muscle diseases. The free base form of the drug has been used to treat congenital myasthenic syndromes and Lambert–Eaton myasthenic syndrome (LEMS) through compassionate use programs since the 1990s and was recommended as a first line treatment for LEMS in 2006, using ad hoc forms of the drug, since there was no marketed form .Amifampridine phosphate has orphan drug status in the EU for Lambert–Eaton myasthenic syndrome and Catalyst holds both an orphan designation and a breakthrough therapy designation in the US. In May 2019 the U.S. Food and Drug Administration (FDA) approved amifampridine tablets under the trade name Ruzurgi for the treatment of Lambert-Eaton myasthenic syndrome (LEMS)

Pathophysiology of LEMS:

In the neuron, voltage-gated calcium channels (VGCCs) play a key role in neurotransmitter release. During normal depolarization of the presynaptic nerve, VGCCs activate, causing an influx of calcium ions initiating the release of ACh from ACh vesicles. ACh then binds to ACh receptors on the postsynaptic neuron producing muscle contractions. Neuronal repolarization occurs when potassium ions efflux through voltage-gated potassium channels. In LEMS, autoimmune antibodies block the P/Q type VGCC in the presynaptic motor neuron, preventing normal calcium ion influx and subsequent ACh release.3 Muscle weakness, loss of tendon reflexes, and autonomic dysfunction are a result of a decreased quantity of ACh in the synapse.

Clinical Picture and Diagnosis of LEMS:

The initial presenting symptom of LEMS is commonly leg weakness. Muscle weakness progresses slowly from the proximal to the distal muscles, eventually affecting the arms, hands, and feet. Patients may also experience dry mouth, erectile dysfunction, constipation, postural hypotension, generalized fatigue, and dysphagia. Diagnosis is made through a combination of history and physical exam, electromyography, and serology testing.

Background

The inhibition of the potassium channel on neuromuscular junctions **causes depolarization of the presynaptic membrane** resulting in prolonged action **potentials and increased release of acetylcholine in the synaptic** cleft. This increase in acetylcholine alleviates some of the neuromuscular dysfunction of myasthenia which is caused by defects in acetylcholine signaling. In small open-label and randomized controlled trials, **amifampridine** was found to alleviate the **myasthenic symptoms** in patients with the rare Lambert-Eaton myasthenic syndrome, but did not reverse the condition or its associated autoimmunity. In 2018, amifampridine was approved as symptomatic therapy for Lambert-Eaton syndrome in adults and is available in scored tablets of 10 mg under the brand name Firdapse. In 2019, amifampridine was approved as symptomatic therapy for Lambert-Eaton syndrome in children and became available as scored 10 mg tablets under the brand name Fuzurgi. The recommended starting dose is 15 to 30 mg in 3 to 4

divided doses daily with dose increases of 5 mg and a maximum total dose of 80 mg daily. A reduced dose is recommended for children weighing less than 45 kilograms. Common side effects are

Lambert–Eaton myasthenic syndrome(LEMS)

In Lambert–Eaton myasthenic syndrome, acetylcholine release is inhibited as antibodies involved in the host response against certain cancers cross-react with Ca2+ channels on the pre junctional membrane. Amifampridine works by blocking potassium channel efflux in nerve terminals so that action potential duration is increased. Ca2+ channels can then be open for a longer time and allow greater acetylcholine release to stimulate muscle at the end plate.

About 50-60% of the patients develop more rapidly progressive LEMS and small cell lung cancer, which influences the prognosis. Patients with LEMS develop serum antibodies against presynaptic P/Q-type voltage-gated calcium channels, leading to decreased presynaptic calcium levels and reduced quantal release of acetylcholine, which is mainly responsible for causing symptoms of LEMS. Reduced acetylcholine release at the neuromuscular junction leads to decreased frequency of miniature endplate potentials of normal amplitude, and insufficient acetylcholine levels for the activation of postsynaptic muscle fibers following a single nerve mpulse.

Treatment for (LEMS)

Treatment for LEMS include immunotherapy such as conventional immunosuppression or intravenous immunoglobulins, however such treatments are recommended in patients in whom symptomatic treatment leads to the reduction of the compound muscle action potential (CMAP).

General Information:

The chemical structure of amifampridine phosphate was elucidated by a combination of spectroscopic methods (1H- and 13C-NMR, FT-IR, UV spectroscopy), thermal analysis (Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis) and qualitative phosphate analysis. The solid-state properties of the active substance were measured by X-ray powder diffraction.

- **FIRDAPSE tablets are intended for oral administration only.**
- Amifampridine phosphate has a non - chiral molecular structure.
- Polymorphism has not been observed for the active substance.
- **A 1% aqueous solution of amifampridine phosphate has a pH of 4.4 at ambient conditions.**

Each FIRDAPSE tablet contains 10 mg amifampridine (equivalent to 18.98 mg amifampridine phosphate). The tablet formulation includes the following inactive ingredients: calcium stearate, colloidal silicon dioxide, and microcrystalline cellulose.

Amifampridine Phosphate

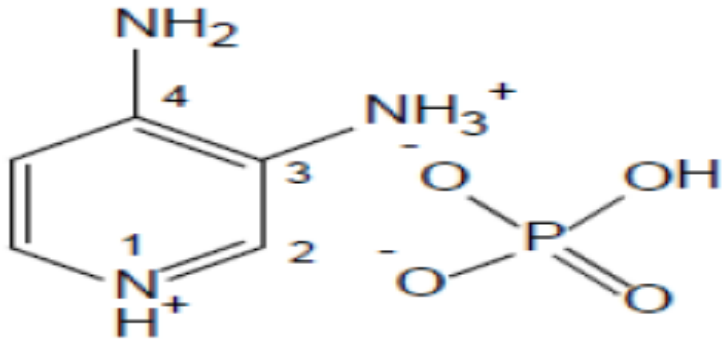


Figure 1: active substance structure

Amifampridine - Physico-chemical Properties.

Drug Class:	**Myasthenia Agents**
Chemical Name:	3,4-Diamino pyridine- phosphate
Molecular Formula	$C_5H_{10}N_3O_4P$ ($C5H7N_3 \times H_3PO_4$).
Apperance	white crystalline powder
Hydrogen Acceptor Count	3
Hydrogen Donor Count	2
Polar Surface Area	64.93 $Å^2$
Rotatable Bond Count	5

Refractivity	33.35 m3·mol-1
Polarizability	10.94 Å3
Number of Rings	1
Water Solubility	159.0mg/mL
Molar Mass	207.1 g/mol
Monoisotopic:	109.063997237
Density	1.0806 (rough estimate)
Melting Point	229 ± 2°C.
Flash Point	135- 357°C
Water Solubility	24mg/ml(20°C)
Solubility	soluble in water, slightly soluble in dimethylsulfoxide, glacial acetic acid and methanol and very slightly soluble in ethanol and dimethylformamide.
Appearance	white color, crystalline powder.
pKa	9.25
Storage Condition	25°C
Refractive Index	1.4186
Action:	Bloking Potassium channel , Cholinergic Agonist.
Receptor:	Acetylcholine
Physical form Availability:	**Solid**
Formulations:	Tablet
Indication:	**1)** Postpartum bleeding 2) Periprocedural hemorrhage in hemophiliacs.
Storage:	Tablet dosage form Store at room temperature away from light and moisture. Keep all medications away from children and pets. Store at 25°C.

Stability: Stability data from commercial batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75 % RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Photostability studies on three batches of the active substance have been reported, with sample having been exposed to 13500 Lux / 1.96 W/m2 at 25 ºC for 102 hours. No significant increase in impurity.
Levels was apparent, but slight darkening of powder was observed and hence, it has been concluded that the active substance is light sensitive.

Pharmacodynamics:
Administration of amifampridine to patients with LES in clinical trials resulted in improvement of the compound muscle action potential (CMAP), muscle function, and quantitative myasthenia gravis (QMG) score. One case of a slight prolongation of the QTc interval in male patient with LEMS and euthyroid Hashimoto's disease treated with 90 mg of amifampridine in combination with 100 mg azathioprine was reported. In vitro, amifampridine was shown to modulate cardiac conduction and induce phasic contractions in different arteries from several species. In addition, it stimulated potassium-evoked dopamine and noradrenaline release in rat hippocampal slices and upregulate acetylcholine release in the brain. It may also potentiate adrenergic and cholinergic neuromuscular transmission in the gatrointestinal tract. In a single pharmacokinetic study, no effect was observed of amifampridine phosphate on cardiac repolarization as assessed using the QTc interval. There were no changes in heart rate, atrioventricular conduction or cardiac depolarization as measured by the heart rate, PR and QRS interval durations.

Mechanism of action:
Amifampridine is a symptomatic treatment that increases acetylcholine concentrations at the neuromuscular junction. It selectively blocks presynaptic fast voltage-gated potassium channels, thereby prolonging cell membrane depolarization and action potential, and augmenting calcium transport into the nerve endings. Increased intracellular calcium enhances the exocytosis of acetylcholine-containing vesicles and enhances impulse transmission at central, autonomic, and neuromuscular synapses.Amifampridine improves muscle strength and resting compound muscle action potential (CMAP) amplitudes with an overall weighted mean difference of 1.69 mV 12.

A- 3,4(DAP- 3,4-Diamino pyridine- Amifampridine)

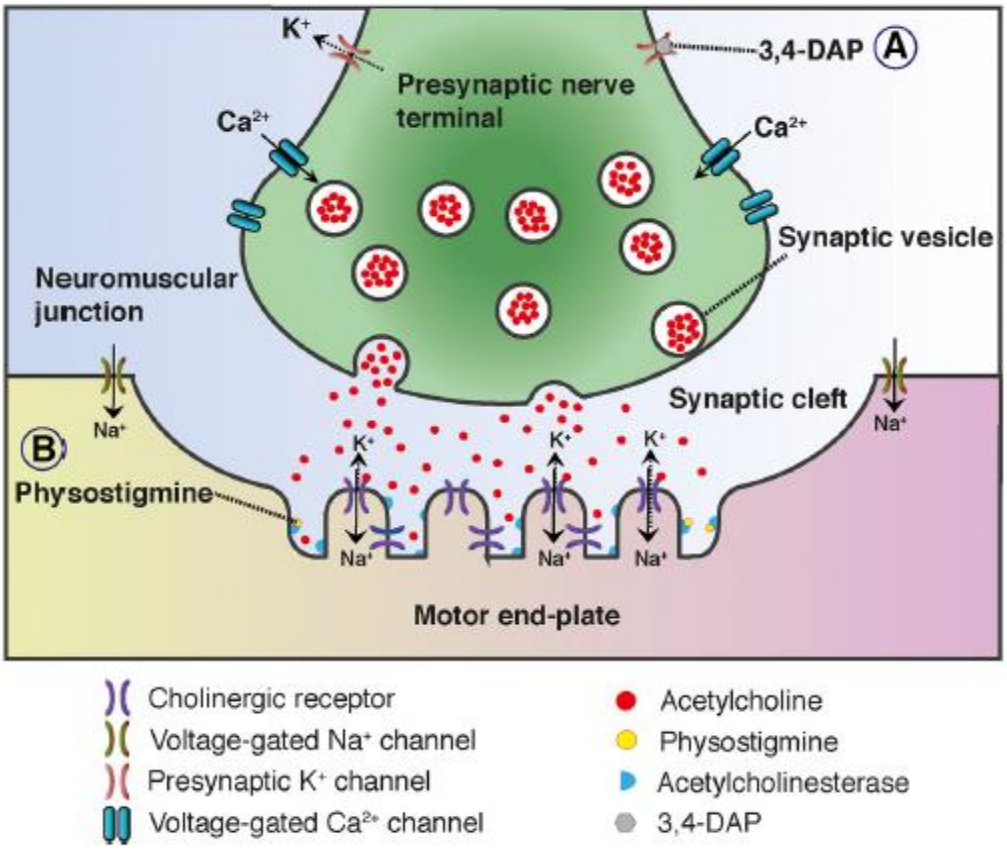


Figure 1. Mechanisms of action for 3,4-DAP and physostigmine. ***A***, 3,4-DAP blocks K^+ channel efflux in presynaptic nerve terminals, resulting in an increased duration of presynaptic action potential. This increases the opening time of Ca^{2+} channels, which induces greater acetylcholine release from presynaptic vesicles. However, 3,4-DAP failed to improve wire-hang times in 4-month *Gars*^{C201R} NMJs. ***B***, Physostigmine inhibits acetylcholinesterase, an enzyme that breaks down acetylcholine in the synaptic cleft. Physostigmine improved wire-hang times in 4-month *Gars*^{C201R} NMJs. Both physostigmine and 3,4-DAP can be used to increase EPC amplitude in 4-month old *Gars*^{C201R} NMJs.

Pharmacological Action:

Recent investigations have challenged the conventional mechanism of action of aminopyridines. First, prior concentration-response studies of aminopyridine action on Kv channels have often been restricted to the use of 4-aminopyridine and yielded an IC50 between 30 μM and 2.5 Mm depending on the types of potassium channels expressed, with a high sensitivity to 4 aminopyridine reported for Kv3 channels (80-μM IC50;). Because 4-aminopyridine crosses the blood–brain barrier better than 3,4-DAP, the latter has been preferred for the treatment of

peripheral neuromuscular diseases. Therapeutic concentrations of 3,4-DAP are predicted to be in the low micromolar range, and 3,4-DAP has been reported to have significant effects on squid giant axon potassium channels at these concentrations. Second, a direct agonistic action of 3,4-DAP on Cav1 type (also called "L-type") channels was reported. However, the clinical relevance of the reported effects of 3,4-DAP on Cav channels was debated because the 3,4-DAP concentrations evaluated in these studies were significantly above blood serum levels found in LEMS treatment conditions. Furthermore, because Cav1 channels usually lack the synaptic protein interaction sites present in Cav2 channels, Cav1 channels are thought to reside outside of synaptic vesicle release sites in the NMJ and therefore are not thought to directly control acetylcholine release (as Cav2 channels do) at healthy synapses. However, it is possible that Cav1 channels may have a minor role at neuromuscular synapses that is revealed under pharmacological conditions, and Cav1 channels may have a compensatory contribution to the control of transmitter release in diseased conditions such as LEMS. Therefore, to investigate the physiological mechanism accounting for the clinical response to 3,4-DAP, we tested the effects of a therapeutic concentration of 3,4-DAP (1.5 μM) on (a) peak currents of Kv3 channels expressed in cells.

Mode of Action:

3,4-DAP effectively inhibits voltage-dependent potassium channels and by this mechanism triggers an increased release of ACh. it was discovered that the direct stimulation of the smooth muscle tonus induced by 3,4-DAP can be partly antagonised by atropine in line with the proposed pharmacological effect of 3,4-DAP, i.e. the increased release of ACh via blockage of presynaptic potassium channels.

Pharmacokinetic:

Systemic exposure to amifampridine is affected by the overall metabolic acetylation activity of NAT enzymes and NAT2 genotype 4. The NAT enzymes are highly polymorphic that results in variable slow acetylator (SA) and rapid acetylator (RA) phenotypes. Slow acetylators are more prone to increased systemic exposure to amifampridine, and may require higher doses for therapeutic efficacy.

Absorption:
Orally-administered Amifampridine is rapidly absorbed in humans to reach the peak plasma concentrations within by 0.6 to 1.3 hours. A single oral dose of 20 mg amifampridine in fasted individuals resulted in mean peak plasma concentrations (Cmax) ranging from 16 to 137 ng/mL. Bioavailability is approximately 93-100% based on recoveries of unmetabolised amifampridine and a major 3-N-acetylated amifampridine metabolite in urine . Food consumption decreases amifampridine absorption and exposure with a decrease in the time to reach maximum concentrations (Tmax) 3. It is approximated that food consumption lowers the Cmax on average by ~44% and lowers AUC by ~20%. based on geometric mean ratios.

Volume of distribution:
In healthy volunteers, the volume of distribution for plasma amifampridine indicated that RUZURGI is a drug with a moderate to a high volume of distribution.After a 2 mg/kg infusion in rats, the volume of distribution at steady-state was 2.8 ± 0.7 L/kg.5 Drug concentrations were highest in organs of excretion, including the liver, kidney, and the gastrointestinal tract, and some tissues of glandular function, such as lacrimal, salivary, mucous, pituitary, and thyroid glands. Concentrations in tissues are generally similar to or greater than concentrations in plasma.
Protein binding:
In vitro human plasma protein binding of amifampridine and 3-N-acetyl amifampridine was 25.3% and 43.3%, respectively.
Metabolism:
Amifampridine is extensively metabolized by N-acetyltransferase 2 (NAT2) to 3-N-acetyl-amifampridine, which is considered an inactive metabolite.
Known N-acetyltransferase 2 (NAT2) Poor Metabolizers
The recommended starting dosage of FIRDAPSE in known N-acetyltransferase 2 (NAT2) poor metabolizers is the lowest recommended initial daily dosage (i.e., 15 mg daily for pediatric patients weighing 45 kg or more and for adults, and 5 mg daily for pediatric patients weighing less than 45 kg) taken orally in divided doses
Route of elimination : Following oral administration, more than 93% of total amifampridine is renally eliminated within 24 hours 3. About 19% of the total renally-excreted dose is in the parent drug form, and about 74-81.7% of the dose is in its metabolite form.
Excretion
Following administration Amifampridine to healthy subjects, 93% to 100% of the administered dose was eliminated in the urine as amifampridine or 3-N-acetyl amifampridine over 24 hours.
Half-life: The average elimination half-life of amifampridine was 3.6 to 4.2 hours and 4.1 to 4.8 hours for the 3-N-acetyl amifampridine metabolite.
Clearance:
Overall clearance of amifampridine is both metabolic and renal; it is primarily cleared from the plasma via metabolism by N-acetylation 12. Following oral administration of a single 20 or 30 mg dose of RUZURGI to healthy volunteers, amifampridine apparent oral clearance (CL/F) was 149 to 214 L/h.
Toxicity: The approximate oral LD50 was >25mg/kg in rats and 100 mg/kg in mice. The approximate intravenous LD50 was 25 mg/kg in both rats and mice 13. Peritoneal and subcutaneous LD50 in mice were 20 mg/kg and 35 mg/kg, respectively 1. There is limited clinical experienced with amifampridine overdose. The manifestations of acute drug overdose may include abdominal pain, and should be responded with discontinuation of treatment and initiation of supportive care with close monitoring of viral signs. There is no specific antidote known for amifampridine. In vitro, amifampridine showed no clinically relevant carcinogenic or genotoxic potential. However, in a 2-year rat study, amifampridine caused small but statistically significant dose-related increases in the incidence of Schwannomas in both genders and of endometrial carcinomas in females. At doses higher than the recommended daily dose for humans, amifampridine caused a dose-related increase in the percentage of pregnant rats with stillborn off spring . Effects on the central and autonomic nervous system, increased liver and kidney weights and cardiac effects (second degree atrioventricular block) were seen in a repeat-dose toxicity studies in rats and dogs.
Hepatotoxicity
Amifampridine has had limited clinical use, but adverse events have been largely neurologic and gastrointestinal. Serum ALT elevations were not reported in the prelicensure studies of amifampridine but were reported as occurring in a small proportion of patients in safety reviews by the Food and Drug Administration. Nevertheless, there have been no reports of clinically apparent liver injury associated with its use. Thus, liver injury from amifampridine must be rare if it occurs at all.
Indication:
Amifampridine is indicated for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients. Nevertheless, at the current time only the Firdapse brand of amifampridine is indicated for the treatment of LEMS in both adult and pediatric patients, while the Ruzurgi brand of amifampridine is indicated for the treatment of LEMS only in patients aged 6 to less than 17 years.

CLINICAL STUDY:

The data generated indicate that, in both species, all indices are of the same order of magnitude and the bioavailability of the base form of 3,4-DAP vs. the phosphate salt is similar. In addition, no significant gender differences were apparent. Hence cross-referring to the non-clinical profile for 3,4-DAP base in the rat and dog can be considered a valid approach.

MDS 266/008, pharmacokinetic indices after a single oral administration of 1 mg/kg 3,4-DAP base or 1.9 mg/kg phosphate salt to Beagle dogs.

Animal (Beagle dogs)	Female (n=1)	Female (n=1)	Male (n=1)	Male (n=1)
Formulation	Base	Salt	Salt	Base
Time Point	Day0	Day 14	Day0	Day14
$t_{1/2}$ (min)	148	135	104	136
T_{max} (min)	15	45	15	30
C_{max} (µg/L)	396	336	442	363
$AUC_{0\text{-}720\ min}$ (min*µg/L)	62960	73230	NA	76534

In phase III clinical trials of adult patients with LEMS, treatment of amifampridine significantly improved symptoms of LEMS compared to placebo with good tolerance. It was demonstrated in clinical studies involving healthy volunteers that the pharmacokinetics and systemic exposure to amifampridine is affected by the genetic differences in N-acetyl-transferase (NAT) enzymes (acetylator phenotype) and NAT2 genotype, which is subject to genetic variation .Slow acetylators were at higher risk for experiencing drug-associated adverse reactions, such as paresthesias, nausea, and headache.

Manufacture, characterisation and process controls

Amifampridine phosphate is synthesized in four main steps using a well-defined starting material with acceptable specifications.The active substance is manufactured by one manufacturing site, with additional sites involved for testing.

The manufacturing process has been described in sufficient detail and the overall control strategy and the risk mitigation measures are adequate to control the process and ensure active substance of intended and consistent quality. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameters have been identified and proven acceptable ranges were established for those process parameters. Intermediates are isolated after each step and are subject to release testing prior to use in the next step.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on the Chemistry of Active Substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Potential genotoxic impurities were addressed; The starting material and intermediates are considered structural alerts for possible genotoxicity and are all controlled as identified impurities in the active substance specification.

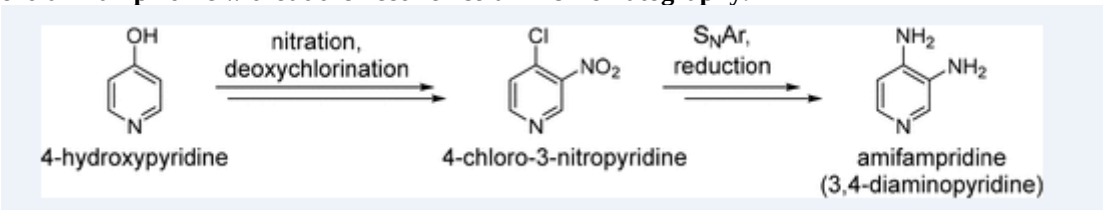
Information in relation to residual solvents has been provided. Residual solvents are sufficiently controlled. Benzene, a possible contaminant in the solvents used, is adequately controlled.

Changes introduced during the development of the manufacturing process have been described in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is comparable to that produced by the proposed commercial process.

The primary packaging material complies with EC directive EC 10/2011 as amended.

Synthesis of AMIFAMPRIDINE(3,4(DAP- 3,4-Diamino pyridine)) :

An efficient synthesis of the exorbitantly priced Lambert–Eaton myasthenic syndrome drug amifampridine was developed and applied in the second-semester undergraduate organic chemistry laboratory. The two-step synthesis entails a nucleophilic aromatic substitution reaction of commercial 4-chloro-3-nitropyridine with methanolic ammonia to afford 4-amino-3-nitropyridine. Subsequent palladium-catalyzed nitro reduction provides amifampridine in high yield and purity. Amifampridine can alternatively be prepared by advanced undergraduate students in four linear steps beginning with 4-hydroxypyridine. Nitration of 4-hydroxypyridine to 4-hydroxy-3-nitropyridine and subsequent treatment with phosphoryl chloride provides the intermediate 4-chloro-3-nitropyridine, which is then subjected to the SNAr and reduction reactions to cleanly afford amifampridine without the need for column chromatography.



Dosage Information

Pediatrics :

Safety of FIRDAPSE(Amifampridine phosphate)was evaluated in pediatric patients in an expanded access program, where 21 pediatric patients received FIRDAPSE for at least 1 year. Adverse reactions reported in pediatric patients were similar to those seen in adult patients, with the exception of clinically significant weight loss in two pediatric patients at doses of 60 mg per day and higher.

The recommended dosage regimen of FIRDAPSE for adults and pediatric patients 6 years of age and older. For pediatric patients, the recommended dosing regimen is dependent on body weight. Dosage should be increased every 3 to 4 days based on clinical response and tolerability.

Recommended Oral Dosage for the Treatment of LEMS in Adults and Pediatric Patients 6 Years of Age and Older

Age and Body Weight	Initial Daily Dosage*	Titration Regimen	Maximum Single Dose	Maximum Total Daily Maintenance Dosage
• Adults (any weight) • Pediatric patients weighing 45 kg or more	15 mg to 30 mg daily, in 3 to 4 divided doses	Increase total daily dosage by 5 mg every 3 or 4 days	20 mg	80 mg Given in divided doses
• Pediatric patients weighing less than 45 kg	5 mg to 15 mg daily, in 3 to 4 divided doses	Increase total daily dosage by 2.5 mg every 3 or 4 days	10 mg	40 mg Given in divided doses

Risk Management Plan:

Safety concerns:

Summary of safety concerns	
Important identified risks	Seizures Food-drug interaction
Important potential risks	Movement disorders Cardiac toxicity including QTc prolongation. Peripheral vascular disorders/Raynaud's phenomenon Respiratory disorders including bronchospasm. Hepatotoxicity Serious gastrointestinal conditions Risk of nerve sheath tumour development (Schwannoma in rats)
Missing information	Limited information on use in patients with renal impairment Lack of information on use in patients with hepatic disease Lack of information on use during pregnancy and lactation Lack of information on potential drug-drug interactions (DDI) (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and nondepolarizing muscle relaxants) Lack of photosafety data

WARNINGS AND PRECAUTIONS

Seizures

FIRDAPSE(Amifampridine Phosphate) can cause seizures. Seizures have been observed in patients without a history of seizures taking FIRDAPSE at the recommended doses, at various times after initiation of treatment, at an incidence of approximately 2%. Many of the patients were taking medications or had comorbid medical conditions that may have lowered the seizure threshold *[see Drug Interactions (7.1)]*. Seizures may be dose-dependent. Consider discontinuation or dose-reduction of FIRDAPSE in patients who have a seizure while on treatment. FIRDAPSE is contraindicated in patients with a history of seizures.

Hypersensitivity

In clinical trials, hypersensitivity reactions and anaphylaxis associated with FIRDAPSE administration have not been reported. Anaphylaxis has been reported in patients taking another aminopyridine; therefore, it may occur with FIRDAPSE. If anaphylaxis occurs, administration of FIRDAPSE should be discontinued and appropriate therapy initiated.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Seizures

Hypersensitivity

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NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity :

In a 104-week carcinogenicity study, oral administration of amifampridine phosphate (0, 15, 48, or 105 mg/kg/day) resulted in an increase in uterine tumors (endometrial carcinoma and combined endometrial adenoma/endometrial carcinoma/squamous cell

carcinoma) at the mid and high doses tested. The low dose, not associated with an increase in tumors, is similar to the maximum recommended human dose (80 mg/day amifampridine) on a body surface area (mg/m^2 basis).

Mutagenesis :

Amifampridine phosphate was negative in the *in vitro* bacterial reverse mutation and *in vivo* rat micronucleus assays. Amifampridine phosphate was positive for clastogenicity in the *in vitro* mouse lymphoma *tk* assay in the absence of metabolic activation.

Impairment of Fertility

Oral administration of amifampridine phosphate (0, 7.5, 22.5, or 75 mg/kg/day) to male and female rats prior to and during mating, and continuing in females throughout organogenesis, produced no adverse effects on fertility. Plasma amifampridine exposure (AUC) at the highest dose tested is approximately 7 times that in humans at the maximum recommended human dose (MRHD) of 80 mg amifampridine/day.

OVERDOSAGE

Overdose with FIRDAPSE was not reported during clinical studies.

In a case report, a 65-year-old patient with LEMS inadvertently received a total daily amifampridine dose of 360 mg/day (more than 4 times the maximum recommended total daily dose) and was hospitalized for general weakness, paresthesia, nausea, vomiting, and palpitations. The patient developed convulsions and paroxysmal supraventricular tachycardia, and four days after admission, experienced cardiac arrest. The patient was resuscitated and ultimately recovered following withdrawal of amifampridine.

Patients with suspected overdose with FIRDAPSE should be monitored for signs or symptoms of exaggerated FIRDAPSE adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

Lactation :

Risk Summary There are no data on the presence of FIRDAPSE in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FIRDAPSE and any potential adverse effects on the breastfed infant from FIRDAPSE or from the underlying maternal condition.

Safety

Amifampridine was well tolerated in 2 phase III trials. No reported adverse effect in either trial was considered to be serious or attributed to treatment. In the first phase III study conducted by Oh et al,14 the most common adverse effects reported were oral (39.6%) and digital paresthesias (34%). Other adverse reactions occurring in >5% of patients included the following: headache, nausea, diarrhea, constipation, dizziness, sore throat, upper respiratory infection, limb pain, and falls. Long-term safety was assessed in 40 patients in an open-label extension phase for up to 2 years, in which no serious adverse effects were observed. In the second phase III trial, adverse effects were reported in 3 patients (23.1%) receiving amifampridine. These adverse effects were mild and included back pain, limb pain, and headache

Amifampridine has been associated with an increased risk of seizures.17 This risk appears to be dose dependent because the majority of patients were receiving ≥90 mg daily.27 Seizures have been reported in approximately 2% of patients.28 Amifampridine is contraindicated in patients with a history of seizures, and the manufacturer recommends caution in patients on medications or with comorbid conditions that may lower seizure threshold. No seizures were reported in either phase III trial; however, patients with a history of seizures were excluded.

FIRDAPSE (Amifampridine phosphate)Dosing:

Instruct patients to take FIRDAPSE exactly as prescribed. Patients should carefully follow the dose escalation schedule provided by their healthcare provider to safely achieve the therapeutic dosage. Inform patients that the tablets may be divided in half at the score, if needed. Instruct patients not to take a double dose to make up for a missed dose. If they require a dosage in less than 5 mg increments, have difficulty swallowing tablets, or require feeding tubes, refer patients and/or caregivers to the Instructions for Use on how to prepare a 1 mg/mL suspension. If the patient requires treatment with the 1 mg/mL FIRDAPSE suspension, advise patients and/or caregivers that supplies required to prepare the suspension may be obtained at their local pharmacy.

Medicinal USE:

I.Congenital Myasthenic Syndromes

- LEMS(, Lambert–Eaton myasthenic syndrome)

LABELLING: **FIRDAPSE (Amifampridine phosphate)**

MEDICATION GUIDE
FIRDAPSE® (FIR-dapse)
(amifampridine)
tablets, for oral use

Read this Medication Guide before you start taking FIRDAPSE and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about FIRDAPSE?
FIRDAPSE can cause seizures.

- You could have a seizure even if you never had a seizure before.
- **Do not** take FIRDAPSE if you have ever had a seizure.

Stop taking FIRDAPSE and call your doctor right away if you have a seizure while taking FIRDAPSE.

What is FIRDAPSE?
FIRDAPSE is a prescription medicine used to treat Lambert-Eaton myasthenic syndrome (LEMS) in people 6 years of age and older.
It is not known if FIRDAPSE is safe or effective in children less than 6 years of age.

Do not take FIRDAPSE if you:

- have ever had aseizure.
- are allergic to amifampridine phosphate, or another aminopyridine.

Before you take FIRDAPSE, tell your doctor about all of your medical conditions. including if you:

- are taking another aminopyridine, such as compounded 3,4-diaminopyridine (3,4-DAP)
- have had a seizure
- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if FIRDAPSE will harm your unborn baby. You and your doctor will decide if you should take FIRDAPSE while you are pregnant.
- There is a registry for women who become pregnant during treatment with FIRDAPSE. The purpose of this registry is to collect information about your health and your baby's health. Contact the registry as soon as you learn that you are pregnant, or ask your doctor to contact for you by calling 855-212-5856 (toll free), contacting the Fax number 877-867-1874 (toll free), emailing the Pregnancy Coordinating Center at firdapsepregnancyregistry@ubc.com, or visiting the study website www.firdapsepregnancystudy.com
- are breastfeeding or plan to breastfeed. It is not known if FIRDAPSE passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking FIRDAPSE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I take FIRDAPSE?

- If your dose is less than 5mg, you have trouble swallowing tablets, or a feeding tube is needed, see the detailed Instructions for Use on how to take and prepare a suspension of FIRDAPSE.
- Take FIRDAPSE exactly as your doctor tells you to take it.
- **Do not** change your dose of FIRDAPSE.
- **Do not** stop taking FIRDAPSE without first talking to your doctor.
- FIRDAPSE tablets are scored and can be split if less than a full tablet is need for you to get the right dose.
- FIRDAPSE can be taken with or without food.
- If you miss a dose of FIRDAPSE, skip that dose and take your next dose at your next scheduled dose time. Do not double your dose to make up the missed dose.
- Do not take FIRDAPSE together with other medicines known to increase the risk of seizures.
- If you take too much FIRDAPSE, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of FIRDAPSE?
FIRDAPSE may cause serious side effects, including:

- **Seizures. See "What is the most important information I should know about FIRDAPSE?"**
- **Serious allergic reactions, such as anaphylaxis.** FIRDAPSE can cause serious allergic reactions. Stop taking FIRDAPSE and call your doctor right away or get emergency medical help if you have:
  - shortness of breath or trouble breathing
  - swelling of your throat or tongue
  - hives

The most common side effects of FIRDAPSE include:

- tingling around the mouth, tongue, face, fingers, toes, and other body parts
- upper respiratory infection
- stomach pain
- nausea
- diarrhea
- headache
- increased liver enzymes
- back pain
- high blood pressure
- muscle spasms

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of FIRDAPSE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FIRDAPSE?

- Store FIRDAPSE tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away FIRDAPSE tablets that are out of date or no longer needed.
- Store FIRDAPSE prepared oral suspension in the refrigerator between 36°F to 46°F (2°C to 8°C) between doses for up to 24 hours.
- Safely throw away unused FIRDAPSE oral suspension after 24 hours.

Keep FIRDAPSE and all medicines out of the reach of children.

General Information about the safe and effective use of FIRDAPSE
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FIRDAPSE for a condition for which it was not prescribed. Do not give FIRDAPSE to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk to your doctor or pharmacist. You can ask your pharmacist or doctor for information about FIRDAPSE that is written for health professionals.

What are the ingredients in FIRDAPSE?
Active ingredient: amifampridine
Inactive ingredients: calcium stearate, colloidal silicon dioxide, and microcrystalline cellulose.

Distributed by Catalyst Pharmaceuticals, Inc., Coral Gables, FL 33134
For more information, go to www.YourCatalyst Pathways.com or call 1-833-422-8259

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CONCLUSION

Amifampridine is effective for the management of LEMS symptoms. Relevance to Patient Care and Clinical Practice: With an improved stability profile and decreased dose variability, amifampridine will likely assume the role of first-line management of LEMS. Conclusions: Amifampridine has been shown to improve symptoms of LEMS and is generally well tolerated.

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