PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr FIRDAPSE®

Amifampridine tablets

Tablets, 10 mg amifampridine (as 18.98 mg amifampridine phosphate), oral

Potassium Channel Blocker

KYE Pharmaceuticals Inc.
2233 Argentia Rd., East Tower, Suites 302 & 302A
Mississauga
Ontario
Canada
L5N 2X7

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FIRDAPSE® (amifampridine) is indicated for the symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.

FIRDAPSE® should only be prescribed by health professionals who have experience in the treatment of LEMS, are knowledgeable of the efficacy and safety profile of this drug, and are able to discuss benefits/risks of treatment with patients.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): In clinical studies of FIRDAPSE® (Studies 1-2), 25.4% (16 of 63) of LEMS patients receiving FIRDAPSE® were ≥ 65 years of age.
These studies did not include sufficient number of patients aged 65 years and over to determine whether its safety and efficacy differs in elderly patients compared to younger patients [see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

2 CONTRAINDICATIONS

Amifampridine is contraindicated in patients:

- who are hypersensitive to this drug or another aminopyridine.
- with a history of seizures.
- who are hypersensitive to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- who are taking other forms of amifampridine or other aminopyridines.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

The dose of FIRDAPSE® should be individually titrated for each patient.

Caution is advised if administering FIRDAPSE® to patients with risk factors for torsade de pointes or in combination with drugs known to prolong the QT interval [see WARNINGS AND PRECAUTIONS, Cardiovascular; OVERDOSAGE; DRUG INTERACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics].

3.2 Recommended Dose and Dosage Adjustment

Adult patients 18 years of age and older diagnosed with LEMS:

- The recommended starting dose is 15 mg daily, taken orally in divided doses (3 times daily). If the patient is known to be N-acetyltransferase 2 (NAT2) fast acetylators the starting dose can be 30 mg.
- The dosage can be increased by 5 mg daily every 3 or 4 days; the patient should be closely monitored for adverse reactions
- The maximum recommended total daily dosage is 80 mg
- The maximum single dose is 20 mg.

Pediatric Patients

Health Canada has not authorized an indication for pediatric use [see INDICATIONS, Pediatrics].

Elderly Patients

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Patients with Renal Impairment

Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine, and exposure of amifampridine is higher in subjects with renal impairment. Therefore patients with renal impairment should be closely monitored for adverse reactions. No dosage recommendation for FIRDAPSE® can be made for patients with end-stage renal disease [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Patients with Hepatic Impairment

FIRDAPSE® has not been studied in controlled clinical trials of patients or volunteers with any degree of hepatic impairment. FIRDAPSE® is extensively metabolized and hepatic impairment can slow its metabolism resulting in higher plasma drug levels. Therefore, when initiating FIRDAPSE® in patients with any degree of hepatic impairment monitor for adverse reactions. Consider dosage modification or discontinuation of FIRDAPSE® for patients with hepatic impairment as needed based on clinical effect and tolerability [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Known N-acetyltransferase 2 (NAT2) Slow Acetylators

Exposure of FIRDAPSE® is increased in patients who are N-acetyltransferase (NAT2) slow acetylators [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions]. Therefore, when initiating FIRDAPSE®, known NAT2 poor acetylators should be closely monitored for adverse reactions.

3.3 Administration

FIRDAPSE® is to be taken orally in divided doses 3 to 4 times per day. FIRDAPSE® may be taken without regard to food.

3.4 Missed Dose

If a dose is missed, treatment should be continued with the next dose as planned, patients should not take double or extra doses.

4 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. ECG monitoring is recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1- Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 10 mg Each scored tablet contains 10 mg amifampridine which is equivalent to 18.98 mg amifampridine phosphate	calcium stearate colloidal silicon dioxide microcrystalline cellulose

FIRDAPSE® 10 mg tablets are white to off white, round, and functionally scored. Each tablet is debossed on the non-scored side with “CATALYST” and on the scored side with “211” above the score and “10” below the score. Tablets can be divided in half at the score.

FIRDAPSE® tablets are supplied in child resistant bottles containing 240 tablets.

6 WARNINGS AND PRECAUTIONS

Carcinogenicity

In a 2-year dietary carcinogenicity study in rats, low incidences of benign and malignant schwannomas were observed in males and/or females at all dose levels and there was an increased incidence of endometrial adenomas and carcinomas tumors at the mid and high dose levels [see NON-CLINICAL TOXICOLOGY]. The significance of these tumors for patients is unknown. Schwannomas in humans are usually benign.

Cardiovascular

QTc Interval Prolongation

FIRDAPSE® can cause QTc interval prolongation in N-acetyltransferase 2 slow acetylators [see ACTION AND CLINICAL PHARMACOLOGY, Electrocardiography; DRUG INTERACTIONS, Drugs that Prolong the QTc Interval]. Drugs that prolong the QTc increase the risk of torsade de pointes, a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes can be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Caution should be observed if FIRDAPSE® is administered to patients who have risk factors for torsade de pointes. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; congenital long QT syndrome; cardiac disease (e.g., myocardial infarction, heart failure); history of arrhythmias; bradycardia (<50 beats per minute); and electrolyte disorders. Hypokalemia, hypocalcemia, and hypomagnesemia should be corrected prior to initiation or continuation of FIRDAPSE®.

Endocrine and Metabolism

Exposure of FIRDAPSE® is increased in patients who are N-acetyltransferase (NAT2) slow acetylators [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions]. Therefore, when initiating FIRDAPSE®, known NAT2 poor acetylators should be closely monitored for adverse reactions [see DOSAGE AND ADMINISTRATION].

Hepatic/Biliary/Pancreatic

The effects of FIRDAPSE® have not been studied under controlled conditions in patients or volunteers with any degree of hepatic impairment. Since FIRDAPSE® is extensively metabolized/acetylated by N-acetyltransferase 2 (NAT2), and hepatic impairment may cause an increase in exposure [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions]. Therefore, when initiating FIRDAPSE®, patients with hepatic impairment should be closely monitored for adverse reactions [see DOSAGE AND ADMINISTRATION].

Immune

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.

Neurologic

Seizures/Convulsions

FIRDAPSE® 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. FIRDAPSE® should be used with caution in combination with drugs that are known to lower seizure threshold [see Drug-Drug Interactions]. 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 [see CONTRAINDICATIONS].

Driving and Operating Machinery

Due to adverse reactions such as drowsiness, dizziness, seizures and blurred vision, amifampridine may have minor or moderate influence on the ability to drive or use machines. Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Renal

Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine, and exposure of amifampridine is higher in subjects with renal impairment [see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions]. Therefore, when initiating FIRDAPSE®, patients with renal impairment should be closely monitored for adverse reactions [see DOSAGE AND ADMINISTRATION].

Respiratory

Based upon its pharmacodynamic properties, amifampridine could exacerbate asthma symptoms. Patients with asthma should be treated so their symptoms are controlled. In postmarket settings, cases of bronchospasms, asthma attacks in asthmatic patients and patients with a history of asthma have been reported, some of them were serious.

6.1 Special Populations

6.1.1 Pregnant Women

FIRDAPSE® should not be used during pregnancy. Women of childbearing potential must use effective contraception during FIRDAPSE® treatment. There are no adequate and well-controlled studies with FIRDAPSE® in pregnant women to inform a drug-associated risk of

adverse developmental outcomes.

Amifampridine administered during organogenesis had no effect on embryo-fetal development in rabbits. In rats, amifampridine administered during pregnancy and lactation resulted in an increase in the number of mothers delivering still-born offspring [see NON-CLINICAL TOXICOLOGY].

Pregnancy Registry

A pregnancy registry has been established to collect information about the effect of FIRDAPSE® exposure during pregnancy. Healthcare professionals are encouraged to register patients, and pregnant women are encouraged to enroll themselves by visiting the website www.firdapsepregnancystudy.com or by calling 1-855-212-5856 (toll free).

6.1.2 Breast-feeding

It is unknown if amifampridine is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

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.

In lactating rats, amifampridine was excreted in milk and reached levels similar to those in maternal plasma.

6.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

Clinical studies of FIRDAPSE® did not include sufficient number of patients aged 65 years and over to determine whether safety and tolerability differs in elderly patients compared to younger patients. In clinical studies (Studies 1-2), 25.4% (16 of 63) of LEMS patients receiving FIRDAPSE® were ≥ 65 years of age.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

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

- Seizures [see Warnings and Precautions]
- Hypersensitivity [see Warnings and Precautions]

The most commonly reported (>10%) adverse reactions associated with FIRDAPSE® for healthy

individuals and LEMS patients receiving FIRDAPSE® in clinical studies include peripheral and perioral paresthesia; dizziness; headache; and oral hypoesthesia.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In controlled and uncontrolled trials (Study 1 and 2) in patients with LEMS, 63 patients were treated with FIRDAPSE®, including 40 patients treated for more than 6 months, and 39 patients treated for more than 12 months. In an expanded access program, 139 patients with LEMS were treated with FIRDAPSE®, including 102 patients treated for more than 6 months, 77 patients treated for more than 12 months, and 53 patients treated for more than 18 months.

Study 1 was a double-blind, placebo-controlled, randomized discontinuation study in adults with LEMS. Following an initial open-label run-in phase (up to 90 days), patients were randomized to either continue FIRDAPSE® treatment or transition to placebo, for a 14-day double-blind phase. Following final assessments, patients were allowed to resume FIRDAPSE® treatment for up to 2 years (open label long-term safety phase of the study).

During the open-label run-in phase of Study 1, 53 patients received FIRDAPSE® for an average of 81 days at a mean daily dosage of 50.5 mg/day. The mean patient age was 52.1 years and 66% were female. There were 42 patients who had no prior exposure to amifampridine at the initiation of this study. Table Table 2 shows adverse reactions with an incidence of 5% or greater occurring in the 42 LEMS patients newly initiated on treatment with FIRDAPSE® during the run-in phase of the study.

Table 2 – Summary of Adverse Reactions in ≥5% of LEMS Patients Newly Treated with FIRDAPSE® in Study 1

	FIRDAPSE® N = 42 %
Paraesthesia*	62
Upper respiratory tract infection	33
Abdominal pain	14
Nausea	14
Diarrhea	14
Headache	14
Elevated liver enzymes**	14
Back pain	14
Hypertension	12
Muscle spasms	12
Dizziness	10
Asthenia	10
Muscular weakness	10
Pain in extremity	10
Cataract	10
Constipation	7
Bronchitis	7
Fall	7
Lymphadenopathy	7

* Includes paresthesia, oral paresthesia and oral hypoesthesia
**Includes elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gammaglutamyl transferase (GGT)

In the overall population treated in Study 1 (n=53), including the double-blind phase and the 2-year open-label long-term safety phase, additional adverse reactions occurring in at least 5% of the patients included: dyspnea, urinary tract infection, gastro esophageal reflux, insomnia, peripheral edema, pyrexia, viral infection, blood creatine phosphokinase increase, depression, erythema, hypercholesterolemia, and influenza. These patients received a mean daily dosage of 66 mg of FIRDAPSE®.

7.3 Less Common Clinical Trial Adverse Reactions

Eye disorders: blurred vision, diplopia
Gastrointestinal: vomiting
Nervous System: cholinergic syndrome, disturbance in attention, dysgeusia
Psychiatric disorders: anxiety, laziness
Skin and subcutaneous disorders: cold sweat, hyperhidrosis
Vascular disorders: cold extremities

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In LEMS patients newly treated with FIRDAPSE® in Study 1, elevated liver enzymes alanine (including aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gammaglutamyl transferase (GGT)) were observed in 6 individuals (14%) (Table 2). Blood creatine kinase increase and hypercholesterolemia were also reported.

7.5 Clinical Trial Adverse Reactions (Pediatrics)

FIRDAPSE® has not been studied in pediatric patients.

7.6 Post-Market Adverse Reactions

The following events have been reported during post-marketing surveillance.

Cardiovascular:arrhythmias, palpitations
Eye disorders: photophobia
General Disorders: malaise, weight loss
Gastrointestinal: dysphagia
Nervous System: myoclonia, drowsiness, seizure
Respiratory, thoracic and mediastinal disorders: asthma attack in patients with a history of asthma, bronchial hypersecretion, cough, bronchospasm
Vascular disorders: Raynaud's syndrome

8 DRUG INTERACTIONS

8.1 Overview

Specific drug interaction studies have not been conducted with FIRDAPSE®.

8.2 Drug-Drug Interactions

No clinical studies of interactions with other medicines have been performed. However, based on the pharmacodynamic properties of FIRDAPSE® and case reports, the following should be used with close observation.

Drugs that Lower Seizure Threshold

The concomitant use of FIRDAPSE® and drugs that lower seizure threshold may lead to an increased risk of seizures [see Warnings and Precautions]. The decision to administer FIRDAPSE® concomitantly with drugs that lower the seizure threshold should be carefully considered in light of the severity of the associated risks. These substances include most antidepressants (tricyclic antidepressants, selective serotonin uptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, bupropion and tramadol.

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.

Drugs that Prolong the QTc Interval

Caution should be observed if FIRDAPSE® is administered with drugs that can prolong the QTc interval because of potential additive effects [see WARNINGS AND PRECAUTIONS, Cardiovascular; OVERDOSAGE; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology]. Current lists of QTc-prolonging drugs should be consulted.

Drug that Can Reduce Serum Electrolytes

Caution should be observed if FIRDAPSE® is administered with drugs that can decrease serum levels of potassium, magnesium, and/or calcium because of potential augmentation of the QTc prolongation effect [see WARNINGS AND PRECAUTIONS, Cardiovascular; OVERDOSAGE; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology]. Drugs that can decrease serum electrolyte levels include, but are not limited to, loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

8.3 Drug-Food Interactions

Amifampridine may be administered with or without food.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The mechanism by which amifampridine exerts its therapeutic effect in LEMS patients has not been fully elucidated. In vitro, amifampridine at high concentrations is a voltage-gated potassium (K+) channel blocker.

9.2 Pharmacodynamics

Cardiac Electrophysiology

In a double-blind, randomized, placebo- and positive-controlled crossover ECG assessment study in healthy subjects of N-acetyltransferase 2 slow acetylator genotype (N=52), amifampridine phosphate was administered at single doses of 30 mg and 60 mg (1.5X and 3X multiples of the maximum recommended single dose of 20 mg). The maximum differences from placebo in the mean change from baseline QTcF interval were 4.2 ms (90% CI 1.7, 6.8) at 2 h

post-dosing for the 30 mg dose and 5.5 ms (90% CI 2.8, 8.1) at 4 h post-dosing for the 60 mg dose. [see WARNINGS AND PRECAUTIONS, Cardiovascular; OVERDOSAGE: DRUG INTERACTIONS, Drugs that Prolong the QTc Interval].

Amifampridine phosphate was also associated with a decrease in heart rate. The maximum differences from placebo in mean change from baseline heart rate were -5.4 bpm (90% CI -7.3, -3.5) at 1.25 h post-dosing for the 30 mg treatment and -4.9 bpm (90% -6.8, -3.0) at 1.5 and 2 h post-dosing for the 60 mg treatment.

The mean (SD) C_{max} values for amifampridine were 72.1 (33.3) ng/mL for the 30 mg single dose treatment and 137 (49.2) ng/mL for the 60 mg single dose treatment, which were comparable to those for the maximum recommended clinical dose of 20 mg 4 times daily (QID) Q4h in N-acetyltransferase 2 slow acetylators [see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics].

9.3 Pharmacokinetics

The pharmacokinetics of amifampridine are similar between healthy individuals and LEMS patients. Following single and multiple doses, AUC, C_{max} and C_{min} were highly variable between individuals. FIRDAPSE® exposure increased proportionally with dose across the range of 20 mg to 80 mg single oral doses.

At any given dose, the systemic exposure (C_{max} and AUC) depends on the N-acetyltransferase (NAT) phenotype. Individuals who are fast (or rapid) acetylators have an approximately 3.5-to 4.5-fold lower mean peak concentration (C_{max}) and 5.6-to 9-fold lower AUC of amifampridine when compared to slow acetylators.

Table 3 - Summary of Amifampridine Pharmacokinetic Parameters in Healthy Subjects Administered a Single Dose of 10 mg

Single Dose (10 mg) Mean	C_{max} (ng/mL)	T_{max} (hours)	$t_{½}$ (hours)	$AUC_{0-\infty}$ (ng·h/mL)	CL (L/h)	Vd (L)
Fast acetylators	9.91	0.805	1.21	11.1	920	1575
Slow acetylators	34.4	1.14	2.60	68.9	150	577

In a multiple-dose study, healthy subjects who received the maximum recommended dose of amifampridine (20 mg amifampridine, 4 times daily [QID], Q4 h) had mean C_{max} values that ranged between 13.3 and 24.4 ng/mL in fast acetylators and between 67.1 and 97.1 ng/mL in slow acetylators on Days 1, 3 and 4 of dosing.

Absorption: Amifampridine peak plasma concentration is reached 20 minutes to 1 hour after administration. A high-fat, high-calorie meal decreased the rate of amifampridine exposure (C_{max}) by 44% and the extent of exposure (AUC_T) by 20% when compared to administration under fasting conditions. This decreased exposure is not considered to be clinically significant. Amifampridine may be administered without regard to food.

Distribution: Data from in vitro studies in human plasma show [14C] amifampridine phosphate was not highly bound to plasma protein with percentage of unbound ranging from 88.0 to 91.2% depending on the concentration.

Metabolism: Amifampridine is extensively metabolized by N-acetyltransferase 2 (NAT2) to 3-N-acetyl-amifampridine, which is considered an inactive metabolite.

Elimination: Amifampridine is eliminated primarily through metabolism to 3-N-acetyl-amifampridine and to a smaller extent through the kidneys. The terminal half-life ranges from 1.8 to 2.5 hours in healthy subjects. Following administration of FIRDAPSE® 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.

Special Populations and Conditions

Pediatrics: Pharmacokinetics in pediatric patients have not been established.

Geriatrics: In clinical studies (Studies 1-2), 25.4% (16 of 63) of LEMS patients receiving FIRDAPSE® were ≥ 65 years of age.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

Pregnancy and Breast-feeding: No studies in pregnant women have been conducted with FIRDAPSE®. It is not known if FIRDAPSE® is secreted in human milk.

Genetic Polymorphism: Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE® metabolism. Poor acetylators, also referred to as “slow acetylators” (i.e., carriers of two reduced function alleles), have 3.5-to 4.5-fold higher C_{max}, and 5.6-to 9-fold higher AUC than fast acetylators (i.e., carriers of two normal function alleles). Therefore, when initiating FIRDAPSE®, known NAT2 poor acetylators should be closely monitored for adverse reactions [see Dosage and Administration]. In the general population, the NAT2 poor acetylator phenotype prevalence is 40–60% in the White and African American populations, and is 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).

Ethnic Origin: In a population PK analysis, including healthy subjects and patients, race was not found to influence the oral clearance of amifampridine.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of FIRDAPSE® has not been studied. FIRDAPSE® is extensively metabolized by N-acetyltransferase 2 (NAT2) and hepatic impairment may cause an increase in exposure. Therefore, when initiating FIRDAPSE® in patients with any degree of hepatic impairment monitor for adverse reactions

[see DOSAGE AND ADMINISTRATION]. Consider dosage modification or discontinuation of FIRDAPSE® for patients with hepatic impairment as needed based on clinical effect and tolerability.

Renal Insufficiency: Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine, and exposure of amifampridine is higher in subjects with renal impairment. Pharmacokinetic data are available from a study of 24 otherwise healthy subjects with impaired renal function who received a single 10 mg dose of FIRDAPSE®. The exposure of amifampridine (measured as AUC) was 2-to 3-fold higher in subjects with moderate (CLcr 30-59 mL/min) or severe (CLcr 15-29 mL/min) renal impairment than in subjects with normal renal function (CLcr greater than or equal to 90 mL/min). Compared with subjects with normal renal function, subjects with mild renal impairment (CLcr 60-89 mL/min) had a 36% increase in exposure. Therefore, when initiating FIRDAPSE®, patients with renal impairment should be closely monitored for adverse reactions [see DOSAGE AND ADMINISTRATION]. C_{max} was marginally affected by renal impairment.

10 STORAGE, STABILITY AND DISPOSAL

FIRDAPSE® tablets are stored at room temperature 15 to 30°C (59 to 86°F). Do not use beyond the date stamped on the label.

11 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

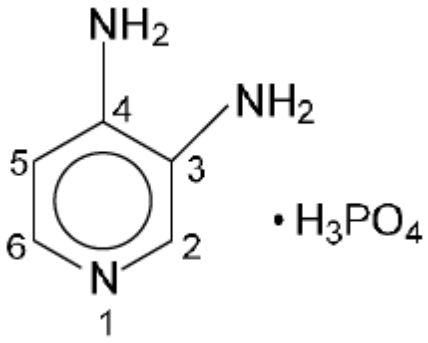
Proper name: amifampridine phosphate

Chemical name: 3,4-diaminopyridine phosphate

Molecular formula and molecular mass of amifampridine phosphate: Molecular formula of $C_5H_7N_3 \bullet H_3PO_4$ and molecular weight of 207.1

Molecular formula and molecular mass of amifampridine free base: Molecular formula of $C_5H_7N_3$ and molecular weight of 109.1

Structural formula of amifampridine phosphate:



Physicochemical properties: Amifampridine phosphate is a white, crystalline powder that is freely soluble in water, and slightly soluble in solvents ethanol, methanol and acetic acid. A 1% aqueous solution of amifampridine phosphate has a pH of 4.4 at ambient conditions.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The efficacy of FIRDAPSE® for the treatment of LEMS was demonstrated in two randomized, double-blind, placebo-controlled discontinuation clinical studies. A total of 64 adults (age 21 to 88 years) with LEMS were enrolled in the double-blind phase (Study 1 and Study 2). The studies enrolled patients with a confirmed diagnosis of LEMS, based on either neurophysiology studies or a positive anti-P/Q type voltage-gated calcium channel antibody test. Patients were required to be on an adequate and stable dosage (30 to 80 mg daily) of amifampridine phosphate prior to entering the randomized discontinuation phases of both studies.

The two co-primary efficacy endpoints in both studies were the change from baseline to the end of the discontinuation period in the Quantitative Myasthenia Gravis (QMG) score and in the Subject Global Impression (SGI) score.

The QMG is a 13-item physician-rated categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale, where a score of 0 represents no weakness, and a score of 3 represents severe weakness (total score 0-39). Higher scores represent greater impairment.

The SGI is a 7-point scale on which patients rated their global impression of the effects of the study treatment on their physical well-being. Lower scores on the SGI represent lower perceived benefit with the study treatment.

Table 4 summarizes the patient demographics from the two pivotal trials. In Study 1, patients had a median age of 54 years (range: 21 to 88 years), 61% were female, and 90% were White. Eighty-four percent of patients had a diagnosis of autoimmune LEMS, and 16% of patients had a diagnosis of paraneoplastic LEMS. In Study 2, patients had a median age of 55.5 years (range: 31 to 75 years), 62% were female, and 88% were White. Seventy-seven percent of patients had a diagnosis of autoimmune LEMS, and 23% of patients had a diagnosis of paraneoplastic LEMS.

Table 4 - Summary of Patient Demographics for the Pivotal Clinical Trials in LEMS

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N)[a]	Mean Age (Range)	Sex
1	Double-blind, placebo-controlled, randomized discontinuation	15 to 80 mg per day, oral administration Open label run-in of up to 91 days Double-blind treatment duration of 14 days	38	51.5 years (21-88)	15 males (39.5%) 23 females (60.5%)
2	Double-blind, placebo-controlled, randomized discontinuation	30 to 80 mg per day, oral administration Double-blind treatment duration of 4 days	26	54.2 years (31-75)	10 males (38.5%) 16 females (61.5%)

[a] Number of subjects entering the double-blind phase of the study.

13.2 Study Results

Study 1

After an initial open-label run-in phase, 38 patients were randomized in a double-blind fashion to either continue treatment with FIRDAPSE® (n=16) or to a downward titration to placebo (n=22) over 7 days. Following the downward titration period, patients remained on blinded FIRDAPSE® or placebo for 7 more days. Efficacy was assessed at Day 14 of the double-blind period. Patients were allowed to use stable dosages of peripherally acting cholinesterase inhibitors or oral immunosuppressants. Twenty-six percent of patients randomized to FIRDAPSE® were receiving cholinesterase inhibitors, versus 36% in the placebo group, and 28% of patients

randomized to FIRDAPSE® were receiving oral immunosuppressant therapies, versus 34% in the placebo group.

During the double-blind period (from Baseline to Day 14), the QMG scores tended to worsen in both treatment groups, but there was significantly greater worsening in the placebo group than in the FIRDAPSE® group (p=0.045). Similarly, the SGI score tended to worsen in both treatment groups during the double-blind period, but there was significantly greater worsening in the placebo group than in the FIRDAPSE® group (p=0.003), as summarized in Table 5. These results indicate that in Study 1, patients randomized to placebo had a significantly greater worsening of muscle weakness and of global impression of the effects of the study treatment on their physical well-being, compared to patients who continued FIRDAPSE® in the double-blind period.

Table 5 - Results of Study 1 in LEMS

Primary Endpoints	FIRDAPSE® N = 16[a]	Placebo N = 21[a]
QMG Scores[b]		
Baseline (Mean)	6.4	5.6
Change from Baseline (LS Mean)	0.4	2.2
FIRDAPSE®-placebo Treatment Difference (LS Mean (95% CI))	1.7 (-3.4, -0.0)	
p-value[d]	0.045	
SGI Scores[c]		
Baseline (Mean)	5.6	5.9
Change from Baseline (LS Mean)	-0.8	-2.6
FIRDAPSE®-placebo Treatment Difference (LS Mean (95% CI))	1.8 (0.7, 3.0)	
p-value[d]	0.003	

LS Mean = Least Squares Mean

a. Number of subjects who completed the double-blind phase of the study
b. QMG Score range 0 (no impairment) to 39 (worst impairment)
c. SGI Score range 0 (least perceived benefit) to 7 (most perceived benefit)
d. Pairwise contrast at Day 14 from mixed-effects model with repeated measures.

Study 2

Patients enrolled from an open-label expanded access program on stable treatment with FIRDAPSE® were randomized 1:1 in a double-blind fashion to either continue treatment with FIRDAPSE® (n=13) or change to placebo (n=13) for 4 days. Efficacy was assessed at the end

of the 4-day double-blind discontinuation period. Patients were allowed to use stable doses of peripherally acting cholinesterase inhibitors or corticosteroids. Sixty-one percent of patients randomized to FIRDAPSE® were receiving cholinesterase inhibitors, versus 54% of patients randomized to placebo. Corticosteroid use was similar between FIRDAPSE® and placebo (8%). Patients with recent use of immunomodulatory therapies (e.g., azathioprine, mycophenolate, cyclosporine), rituximab, intravenous immunoglobulin G, and plasmapheresis were excluded from the study.

From Baseline to Day 4, there was significantly greater worsening in the QMG score in the placebo group than in the FIRDAPSE® group (p=0.0004), and also significantly greater worsening in the SGI score in the placebo group than in the FIRDAPSE® group (p=0.0003), as summarized in Table 6. These results indicate that in Study 2, patients randomized to placebo had a significantly greater worsening of muscle weakness and of global impression of the effects of the study treatment on their physical well-being, compared to patients who continued FIRDAPSE® in the double-blind period.

Table 6 - Results of Study 2 in LEMS

Primary Endpoints	FIRDAPSE® N = 13[a]	Placebo N = 13[a]
QMG Scores[b]		
Baseline (Mean)	7.8	8.5
Change from Baseline (LS Mean)	0.00	6.54
FIRDAPSE®-placebo Treatment Difference (LS Mean (95% CI))	-6.54 (-9.78, -3.29)	
p-value[d]	0.0004	
SGI Scores[c]		
Baseline (Mean)	6.1	5.8
Change from Baseline (LS Mean)	-0.64	-3.59
FIRDAPSE®-placebo Treatment Difference (LS Mean (95% CI))	2.95 (1.53, 4.38)	
p-value[d]	0.0003	

LS Mean = Least Squares Mean

a. Number of subjects who completed the double-blind phase of the study
b. QMG Score range 0 (no impairment) to 39 (worst impairment)
c. SGI Score range 0 (least perceived benefit) to 7 (most perceived benefit)
d. Pairwise contrast at Day 14 from mixed-effects model with repeated measures.

14 NON-CLINICAL TOXICOLOGY

General Toxicology

In acute and chronic studies, central and autonomic nervous system toxicities were observed related to the exaggerated pharmacology of amifampridine phosphate. CNS and respiratory clinical signs in both rats and dogs included: tremors, convulsion, non-responsiveness to stimuli, stiffness of limbs, outstretched limbs, hyperesthesia, and/or labored breathing. Mortality was observed at high doses (53 mg/kg in mice, 40 mg/kg in rats and 4 mg/kg in dogs).

In a chronic repeat-dose toxicity study in rats, amifampridine phosphate was administered daily (three times a day) for 26 weeks at dose levels up to 40 mg/kg/day (free base equivalent). At the highest dose, amifampridine treatment was associated with the development of non-specific neurological findings and acinar cell hypertrophy in the submandibular salivary glands. Based on the findings in this study, it was concluded that the NOAEL for amifampridine was 12 mg free base/kg/day which is 50% higher then the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area (mg/m^2 basis).

In a chronic repeat-dose toxicity study in dogs, amifampridine phosphate was administered daily (three times a day by oral capsule) for 9 months at amifampridine free base dose levels of 0.5, 1 and 2 mg/kg/day. Dose-dependent clinical observations included sneezing, tremors, seizures, hypersalivation, lip-licking, and squinty eyes, which were found most often for the mid and high dose levels. Three high dose dogs developed signs of seizures or seizure like activity. There was no mortality or moribundity during the study. There were no amifampridine-related findings for body weight, food consumption, ophthalmic examination, ECG evaluation, or clinical pathology findings. At necropsy, there were no gross abnormal findings considered to be amifampridine-related. For the mid and high dose female groups, salivary gland weights were significantly increased compared to controls, but there were no corresponding histopathologic findings reported. The NOAEL for amifampridine was determined to be 0.5 mg free base/kg/day. All findings related to amifampridine exposure for the 1 and 2 mg free base/kg/day groups resolved during the 4-week recovery period. At the NOAEL dose of 0.5 mg free base/kg/day, C_{max} was approximately 75 to 80 ng/mL, and the estimated daily $AUC_{0\text{-}24h}$ was approximately 660 to 680 ng·h/mL, which are comparable to exposures in slow acetylators taking the MRHD. Dogs did not show systemic exposure to the 3-N-acetyl metabolite due to the absence of the enzyme N-acetyltransferase in this species.

Low incidences of myodegeneration and myoregeneration in skeletal muscle, tongue, and larynx were observed in a generally dose dependent manner at dose levels of 1, 3, and 4 mg free base/kg/day and minimal myopathy in skeletal muscles seen at 0.5, 1.3, and 3.3 mg free base/kg/day, but also one control animal, in a pair of 4-week studies in dogs. However, similar findings were not observed in the 39-week chronic dog study, or in rats, and thus the relevance of these findings for patients is uncertain.

Carcinogenicity

In a 104-week rat carcinogenicity study, oral administration of amifampridine phosphate in the diet (8, 25, or 55 mg free base/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 dose levels and a low incidence of mainly malignant schwannomas in males and/or females at all dose levels that was not observed in controls. The low dose, not associated with an increase in uterine tumors, is similar to the MRHD (80 mg/day

amifampridine) on a body surface area (mg/m^2 basis). The relevance of these increased tumor incidences in rats for patients is unknown.

Mutagenesis

Amifampridine phosphate was negative in the in vitro bacterial reverse mutation (with and without metabolic activation) and in vivo rat micronucleus and unscheduled DNA synthesis assays. Amifampridine phosphate was positive for clastogenicity in the in vitro mouse lymphoma tk assay in the absence of metabolic activation.

Reproductive and Development Toxicity

A combination fertility and embryo fetal development study was conducted in rats. Oral administration of amifampridine phosphate (0, 3.9, 12.0, or 39.6 mg free base/kg/day) to male and female rats prior to and during mating, and continuing in females throughout organogenesis to gestation day (GD) 17 had no adverse effects on fertility in either males or females. In this study amifampridine was not teratogenic and had no effect on fetal growth. The NOAEL in this study was approximately 5 times MRHD (80 mg amifampridine) based on a body surface area (mg/m^2).

In the rabbit embryo fetal toxicity study, amifampridine phosphate at 4.74, 15.9 or 30 mg free base/kg/day was administrated orally from GD 7-20. Amifampridine at 4.74 mg/kg/day did not cause any maternal toxicity whereas 30 mg/kg/day resulted in severe CNS toxicities and decreased body weight gain and food consumption with moribundity/mortality of five animals. Amifampridine had no effect on embryo fetal development which included evaluations for external, visceral and skeletal anomalies. The NOAEL for maternal toxicity is at 4.74 mg/kg/day and the NOEL for embryo fetal developmental toxicity is 30 mg/kg/day. The 30 mg/kg/day dose is approximately 7 times MRHD based on a body surface area (mg/m^2).

Peri and postnatal toxicity was evaluated after oral administration of amifampridine phosphate (0, 3.95, 12.0, or 39.6 mg free base/kg/day) to female rats from GD6 of pregnancy and throughout lactation resulted in an increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development in female pups at the mid and high doses tested. The no-effect dose (3.95 mg free base/kg/day) for adverse developmental effects is associated is less than that in humans at the MRHD on a body surface area basis.

Abuse Liability

Amifampridine's abuse liability potential was assessed in rats. There were no indications of drug abuse liability in rats where cocaine was reference used for dependence and benzodiazepine for withdrawal. There are no class specific standards for reference.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrFIRDAPSE®
Amifampridine tablets
10 mg

Read this carefully before you start taking **FIRDAPSE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FIRDAPSE®.**

What is FIRDAPSE® used for?

- FIRDAPSE® is used to treat the symptoms of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

How does FIRDAPSE® work?

It is not fully understood how FIRDAPSE® works. Symptoms are generally improved within several hours of taking FIRDAPSE®.

What are the ingredients in FIRDAPSE®?

Medicinal ingredients: amifampridine phosphate
Non-medicinal ingredients: calcium stearate, colloidal silicon dioxide, microcrystalline cellulose

FIRDAPSE® comes in the following dosage forms:

Tablets containing amifampridine phosphate, equivalent to 10 mg amifampridine

Do not use FIRDAPSE® if:

- You have ever had a seizure
- You are allergic to amifampridine, or another aminopyridine
- You are taking other forms of amifampridine or other aminopyridines, such as compounded 3,4-diaminopyridine (3,4-DAP)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FIRDAPSE®. Talk about any health conditions or problems you may have, including if you:

- Have a known gene that may reduce your ability to break down a drug
- Have had a seizure
- Have kidney problems
- Have liver problems
- Have asthma
- Are pregnant or plan to become pregnant.
    - It is not known if FIRDAPSE® will harm your unborn baby. You should not use FIRDAPSE® if you are pregnant.
    - If you are a woman of child bearing potential you must use effective birth control during your treatment with FIRDAPSE®. A registry for pregnant women exposed to FIRDAPSE® has been established. The purpose of this registry is to collect information about the safety of FIRDAPSE® during pregnancy. Patients are asked to register themselves or have their healthcare provider register for them by visiting the website

www.firdapsepregnancystudy.com or by calling 1-855-212-5856 (toll free).

- Are breastfeeding or plan to breast feed. 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®.

Other warnings you should know about:

- FIRDAPSE® can cause problems with your heart rhythm called QTc prolongation, particularly if you have a known gene that may reduce your ability to break down FIRDAPSE®. You may have no symptoms or you may have dizziness, feeling like your heart has skipped or added a beat, fainting or seizures. If these symptoms continue, they can lead to sudden death. You may be more at risk if you have had or have:
  - a known gene that may reduce your body's ability to break down a drug
  - a heart attack
  - congestive heart failure
  - an irregular heartbeat or heart rhythm
  - a blockage in one or more of your arteries that affects blood flow to your heart
  - an abnormally rapid heart rate
  - heart palpitations (feeling like your heart has skipped a beat or added an extra beat)
  - a family history of sudden cardiac death at less than 50 years of age
  - problems of electrocardiogram (ECG) abnormality called "Long QT syndrome"
  - diabetes
  - imbalances in the electrolytes in your body (potassium, magnesium and calcium)
- FIRDAPSE® can cause blurred vision, dizziness, drowsiness or seizures. Before you drive or operate machinery, know how you feel while taking FIRDAPSE®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FIRDAPSE®:

- Antidepressant medicines
- Mefloquine, a medication to treat malaria
- Tramadol, a medication used to treat pain
- Drugs that can affect the levels of electrolytes (potassium, magnesium and calcium) in your body:
  - Diuretics
  - Laxatives and enemas
  - Certain antibiotics
  - High doses of steroids
- Certain drugs that have an effect on your heart rate, such as:
  - antiarrhythmics (such as flecainide and propafenone)
  - antipsychotics (such as chlorpromazine and haloperidol)
  - antidepressants (such as fluoxetine and amitriptyline)
  - opioids (such as methadone)
  - some antibiotics (such as erythromycin, clarithromycin and ciprofloxacin)
  - antimalarials (such as quinone and chloroquine)
  - antifungals (such as ketoconazole)
  - kinase inhibitors (such as sunitinib)
  - histone deacetylase inhibitors (such as vorinostat)
  - beta-2 adrenoceptor agonists (such as salmeterol)

How to take FIRDAPSE®

- Take FIRDAPSE® exactly as your doctor tells you to take it. Do not change your dose of FIRDAPSE®.
- FIRDAPSE® can be taken with or without food.
- Do not take FIRDAPSE® together with other medicines known to increase the risk of seizures or QT intervals without talking to your doctor.
- FIRDAPSE® tablets have a score line in the middle. This can help you break a tablet in half if you need less than a full tablet to get the right dose.

Usual Dose:

Your dose will be decided by your doctor based on your condition and how you react to FIRDAPSE®. FIRDAPSE® is taken 3 to 4 times a day. Do not take more than 2 tablets of FIRDAPSE® at one time or more than 8 tablets in a 24-hour period.

Overdose:

If you think you have taken too much FIRDAPSE® contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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.

What are possible side effects from using FIRDAPSE®?

These are not all the possible side effects you may feel when taking FIRDAPSE®. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of FIRDAPSE® include:

- Upper respiratory infection
- Stomach pain
- Nausea
- Diarrhea
- Headache
- Increased liver enzymes
- Back pain
- High blood pressure
- Muscle spasms
- Partial loss or total loss of sensation in your mouth

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Parasthesia (tingling around the mouth, tongue, face, fingers, toes and other body parts)	√		
COMMON Dizziness	√		
Abdominal pain	√		
RARE Seizures			√
Allergic reaction (rash, hives, swelling of your throat or tongue, trouble breathing)			√
Difficult breathing, worsening asthma symptoms	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store FIRDAPSE® at room temperature (15°C to 30°C)
- Safely throw away FIRDAPSE® that is out of date or no longer needed.

Keep out of reach and sight of children.

If you want more information about FIRDAPSE®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website the manufacturer's website <www.kyepharma.com>, or by calling 1-888-822-7126.

This leaflet was prepared by:
KYE Pharmaceuticals Inc.
2233 Argentia Rd., East Tower, Suites 302 & 302A
Mississauga
Ontario
Canada
L5N 2X7

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