

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

RECENT MAJOR CHANGES

Indications and Usage (1) 9/2022
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5) 9/2022

INDICATIONS AND USAGE

FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Administer orally in divided doses (3 to 4 times daily). (2.1)
- The recommended starting dosage for adults (any weight) and pediatric patients weighing 45 kg or more is 15 mg to 30 mg daily, in divided doses. (2.1)
 - Dosage can be increased by 5 mg daily every 3 to 4 days. (2.1)
 - The maximum single dose is 20 mg. (2.1)
 - Dosage is not to exceed a maximum of 80 mg daily. (2.1)
- The recommended starting dosage for pediatric patients weighing less than 45 kg is 5 mg to 15 mg daily, in divided doses. (2.1)
 - Dosage can be increased by 2.5 mg daily every 3 to 4 days. (2.1)
 - The maximum single dose is 10 mg. (2.1)
 - Dosage is not to exceed a maximum of 40 mg daily. (2.1)
- The recommended starting dosage for adult and pediatric patients with renal impairment, hepatic impairment, and in known N-acetyltransferase 2 (NAT2) poor metabolizers is the lowest recommended initial daily dosage (2.1, 2.2, 2.3, 2.4)
- For patients with a dosage adjustment of less than 5 mg increments, or who have difficulty swallowing, or require feeding tube, a 1 mg/mL suspension can be prepared. (2.5)

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: Concomitant use may lead to an increased risk of seizures. (7.1)
- Drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors): Concomitant use 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.

Revised: 5/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FIRDAPSE® is indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage regimen of FIRDAPSE for adults and pediatric patients 6 years of age and older is included in Table 1. 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. Titration increments should not exceed those shown in Table 1.

Table 1: 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
<ul style="list-style-type: none">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
<ul style="list-style-type: none">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

*See *Dosage and Administration (2.5)* for a method to achieve these doses

Missed Dose

If a dose is missed, patients should not take double or extra doses.

2.2 Patients with Renal Impairment

The recommended starting dosage of FIRDAPSE in patients with renal impairment [creatinine clearance (CL_{cr}) 15 to 90 mL/min] 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. No dosage recommendation for FIRDAPSE can be made for patients with end-stage renal disease [see *Dosage and Administration (2.1)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

2.3 Patients with Hepatic Impairment

The recommended starting dosage of FIRDAPSE in patients with any degree of hepatic impairment 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 [see *Dosage and Administration (2.1)*, *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*].

2.4 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 [see *Dosage and Administration (2.1)*, *Use in Specific Populations (8.8)*, and *Clinical Pharmacology (12.5)*].

2.5 Administration Instructions

FIRDAPSE can be taken without regard to food.

Preparation of a 1mg/mL Suspension (see the Instructions for Use for full instructions on how to prepare the 1mg/mL suspension)

When patients require a dosage in less than 5 mg increments, have difficulty swallowing tablets, or require feeding tubes, a 1 mg/mL suspension can be prepared (e.g., by placing the required number of tablets in a 50 to 100 mL container, adding 10 mL of sterile water for each tablet, waiting for 5 minutes, and shaking well for 30 seconds).

Crushing the tablets prior to making the suspension is not necessary. After preparation of the suspension, an oral syringe can be used to draw up and administer the correct dose by mouth or by feeding tube.

Storage of 1mg/mL Prepared Suspension

Refrigerate the suspension between doses and shake well before drawing up each dose. The suspension can be stored under refrigeration [between 2°C and 8°C (36°F and 46°F)] for up to 24 hours. Discard any unused portion of the suspension after 24 hours.

3 DOSAGE FORMS AND STRENGTHS

FIRDAPSE tablets contain 10 mg amifampridine and 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.

4 CONTRAINDICATIONS

FIRDAPSE is contraindicated in patients with:

- A history of seizures [see *Warnings and Precautions (5.1)*]
- Hypersensitivity to amifampridine phosphate or another aminopyridine [see *Warnings and Precautions (5.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

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 [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.

5.2 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.

6 ADVERSE REACTIONS

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

- Seizures [see *Warnings and Precautions (5.1)*]
- Hypersensitivity [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Adults

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled clinical trials (Study 1 and 2) in patients with LEMS [see *Clinical Studies (14)*], 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 FIRDAPSE at the initiation of this study. 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. Adverse Reactions in $\geq 5\%$ of LEMS Patients Newly Treated with FIRDAPSE in Study 1

Adverse Reaction	FIRDAPSE
	N=42 %
Paresthesia*	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, oral hypoesthesia

**Includes elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gamma- glutamyl transferase (GGT)

Other Adverse Reactions

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, gastroesophageal 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.

Pediatrics

Safety of FIRDAPSE 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.

7 DRUG INTERACTIONS

7.1 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 (5.1)*]. 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.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FIRDAPSE during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the registry by calling 855-

212-5856 (toll-free), using the Fax number 877-867-1874 (toll-free), by contacting the Pregnancy Coordinating Center at firdapsepregnancyregistry@ubc.com, or by visiting the study website www.firdapsepregnancystudy.com.

Risk Summary

There are no data on the developmental risk associated with the use of FIRDAPSE in pregnant women. In animal studies, administration of amifampridine phosphate to rats during pregnancy and lactation resulted in developmental toxicity (increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development) at doses associated with maternal plasma drug levels lower than therapeutic drug levels (see Animal Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of amifampridine phosphate (0, 7.5, 22.5, or 75 mg/kg/day) to female rats prior to and during mating and continuing throughout organogenesis produced no adverse effects on embryofetal development. 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. Oral administration of amifampridine phosphate (0, 9, 30, or 57 mg/kg/day) to pregnant rabbits throughout organogenesis produced no adverse effects on embryofetal development. The highest dose tested is approximately 7 times the MRHD (80 mg/day amifampridine) on a body surface area (mg/m²) basis.

Oral administration of amifampridine phosphate (0, 7.5, 22.5, or 75 mg/kg/day) to female rats throughout pregnancy and 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 (7.5 mg/kg/day amifampridine phosphate) for adverse developmental effects is associated with a plasma amifampridine exposure (AUC) less than that in humans at the MRHD.

8.2 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.

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

8.4 Pediatric Use

Safety and effectiveness of FIRDAPSE for the treatment of LEMS have been established in pediatric patients 6 years of age and older. Use of FIRDAPSE for this indication is supported by evidence from adequate and well-controlled studies of FIRDAPSE in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients aged 6 years and older [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

Safety and effectiveness in pediatric patients below the age of 6 years have not been established.

8.5 Geriatric Use

Clinical studies of FIRDAPSE did not include a sufficient number of subjects aged 65 and over (19 of 63 patients in Studies 1 and 2) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Dosage and Administration (2.2, 2.3)* and *Drug Interactions (7.2, 7.3)*].

8.6 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 [see *Clinical Pharmacology (12.3)*]. Therefore, in patients with renal impairment, FIRDAPSE should be initiated at the lowest recommended initial daily dosage, and patients should be closely monitored for adverse reactions [see *Dosage and Administration (2.2)*]. Consider dosage modification or discontinuation of FIRDAPSE for patients with renal impairment as needed based on clinical effect and tolerability. The safety, efficacy, and pharmacokinetics of amifampridine have not been studied in patients with end-stage renal disease (CL_{Cr} <15 mL/min or patients requiring dialysis). No dosage recommendation for FIRDAPSE can be made for patients with end-stage renal disease.

8.7 Hepatic Impairment

In patients with any degree of hepatic impairment, FIRDAPSE should be initiated at the lowest recommended initial daily dosage, and patients should be monitored for adverse reactions [see *Dosage and Administration (2.3)*]. Consider dosage modification or discontinuation of FIRDAPSE for patients with hepatic impairment as needed based on clinical effect and tolerability.

8.8 NAT2 Poor Metabolizers

Exposure of FIRDAPSE is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolizers [see *Clinical Pharmacology (12.5)*]. Therefore, initiate FIRDAPSE in patients who are known NAT2 poor metabolizers at the lowest recommended initial daily dosage and monitor for adverse reactions [see *Dosage and Administration (2.4)*]. Consider dosage modification of FIRDAPSE for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability.

10 OVERDOSAGE

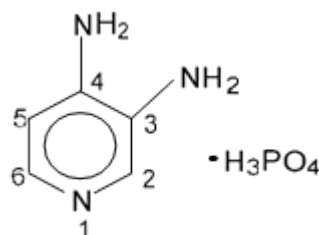
Overdose with FIRDAPSE was not reported during clinical studies.

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.

11 DESCRIPTION

The active ingredient of FIRDAPSE is amifampridine phosphate, which is a voltage-gated potassium channel blocker. Amifampridine phosphate is described chemically as 3,4-diaminopyridine phosphate with a molecular weight of 207.1 and a molecular formula of $C_5H_7N_3 \cdot H_3PO_4$. The structural formula is:



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.

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.

FIRDAPSE tablets are intended for oral administration only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which amifampridine exerts its therapeutic effect in LEMS patients has not been fully elucidated. Amifampridine is a broad-spectrum potassium channel blocker.

12.2 Pharmacodynamics

The effect of FIRDAPSE on QTc interval prolongation was studied in a double blind, randomized, placebo and positive controlled study in 52 healthy individuals who are slow acetylators. At an exposure 2-fold the expected maximum therapeutic exposure of amifampridine, FIRDAPSE did not prolong QTc to any clinically relevant extent.

12.3 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.

Absorption

Amifampridine peak plasma concentration is reached 20 minutes to 1 hour after administration. Food does not have a clinically significant effect on the exposure of amifampridine.

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.

Metabolism

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

Excretion

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.

Specific Populations

Pediatric Patients (6 Years of Age and Older)

A population pharmacokinetic analysis showed that body weight significantly correlates with the clearance of amifampridine; clearance increased with an increase in body weight. A weight-based dosing regimen is necessary to achieve amifampridine exposures in pediatric patients 6 years of age and older, similar to the exposures observed in adults at recommended doses of FIRDAPSE [see *Dosage and Administration (2.1) and Clinical Studies (14)*].

Patients 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 (CL_{cr} 30-59 mL/min) or severe (CL_{cr} 15-29 mL/min) renal impairment than in subjects with normal renal function (CL_{cr} greater than or equal to 90 mL/min). Compared with subjects with normal renal function, subjects with mild renal impairment (CL_{cr} 60-89 mL/min) had a 36% increase in exposure. Therefore, FIRDAPSE should be initiated at the lowest recommended initial daily dosage in patients with renal impairment, and such patients should be closely monitored for adverse reactions [see *Dosage and Administration (2.2) and Use in Specific Populations (8.6)*]. C_{max} was marginally affected by renal impairment.

Patients with Hepatic Impairment

A study was conducted to determine the PK, safety, and tolerability of FIRDAPSE (amifampridine phosphate) administered at 10 mg to subjects with moderate hepatic impairment (N = 7) compared to demographically matched healthy subjects with normal hepatic function (N = 9). The subjects with moderate hepatic impairment had a 22% higher C_{max} and a 33% higher AUC_{inf} for amifampridine than subjects with normal hepatic function. FIRDAPSE was not evaluated in subjects with severe hepatic impairment [see *Dosage and Administration (2.3) and Use in Specific Populations (8.7)*].

12.5 Pharmacogenomics

Genetic variants in the N-acetyltransferase gene 2 (NAT2) affect the rate and extent of FIRDAPSE metabolism. Poor metabolizers, 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 normal metabolizers, also referred to as “fast/rapid acetylators” (i.e., carriers of two normal function alleles). Therefore, FIRDAPSE should be initiated at the lowest recommended initial daily dosage in known NAT2 poor metabolizers, and such patients should be closely monitored for adverse reactions [see *Dosage and Administration (2.4) and Use in Specific Populations (8.8)*]. In the general population, the NAT2 poor metabolizer phenotype prevalence is 40–60% in the White and African American

populations, and in 10–30% in Asian ethnic populations (individuals of Japanese, Chinese, or Korean descent).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

In a 104-week carcinogenicity study in rats, 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/m² basis).

In a 26-week carcinogenicity study in transgenic (Tg.rasH2) mice, oral administration of amifampridine phosphate (0, 2, 7, or 21 mg/kg/day in males and 0, 3, 10, or 30 mg/kg/day in females) resulted in no increase in tumors.

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.

14 CLINICAL STUDIES

The efficacy of FIRDAPSE for the treatment of LEMS was demonstrated in two randomized, double-blind, placebo-controlled discontinuation studies. A total of 64 adults (age 21 to 88 years) with LEMS were enrolled (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 measures of efficacy 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.

A key secondary efficacy endpoint was the clinical global impression improvement (CGI-I) score, a 7-point scale on which the treating physician rated the global impression of change in clinical symptoms. A higher CGI-I score indicates a perceived worsening of clinical symptoms.

Study 1 (NCT01377922)

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.

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.

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 3. 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 3. Change from Baseline to Day 14 in QMG Score and SGI Score in Study 1

Assessment	FIRDAPSE (n=16)	Placebo (n=21)
Primary Endpoints		
QMG Score^a		
Baseline (mean)	6.4	5.6
Change from Baseline (Least Square Mean)	0.4	2.2
FIRDAPSE-placebo Treatment Difference (Least Square Mean (95% CI))	-1.7 (-3.4, -0.0)	
<i>p</i> -value ^c	0.045	
SGI Score^b		
Baseline (mean)	5.6	5.9
Change from Baseline (Least Square Mean)	-0.8	-2.6
FIRDAPSE-placebo Treatment Difference, (Least Square Mean (95% CI))	1.8 (0.7, 3.0)	
<i>p</i> -value ^c	0.003	

- a. QMG Score range 0 (no impairment) to 39 (worst impairment)
- b. SGI Score range 0 (least perceived benefit) to 7 (most perceived benefit)
- c. Pairwise contrast at Day 14 from mixed-effects model with repeated measures.

The CGI-I score was significantly greater for patients randomized to placebo than for patients who continued treatment with FIRDAPSE, with a mean difference between FIRDAPSE and placebo of -1.1 ($p=0.02$), indicating that clinicians perceived a greater worsening of clinical symptoms in patients who were randomized to placebo and discontinued from FIRDAPSE treatment, compared to patients who continued FIRDAPSE in the double-blind period.

Study 2 (NCT02970162)

Patients 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. Patients had a median age of 55.5 years (range: 31 to 75 years), 62% were female, and 88% were white.

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 4. 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 4. Change from Baseline to Day 4 in QMG Scores and SGI Scores in Study 2

Assessment	FIRDAPSE (n=13)	Placebo (n=13)
QMG Scores^a		
Baseline, Mean	7.8	8.5
Change from Baseline, Least Square Mean ^c	0.00	6.54
FIRDAPSE-placebo Treatment Difference, Least Square Mean (95% CI)	-6.54 (-9.78, -3.29)	
<i>p</i> -value ^d	0.0004	
SGI Scores^b		
Baseline, Mean	6.1	5.8
Change from Baseline, Least Square Mean ^c	-0.64	-3.59
FIRDAPSE-placebo Treatment Difference, Least Square Mean (95% CI)	2.95 (1.53, 4.38)	
<i>p</i> -value ^d	0.0003	

- a. QMG Score range 0 (no impairment) to 39 (worst impairment)
- b. SGI Score range 0 (least perceived benefit) to 7 (most perceived benefit)
- c. Change from baseline for QMG total score was modeled as the response, with fixed effects terms for treatment and QMG at Baseline
- d. *p*-value based on the Wilcoxon Rank Sum Test for treatment differences.

The clinical global impression improvement (CGI-I) score was significantly greater for patients randomized to placebo than for patients who continued treatment with FIRDAPSE, with a mean difference between FIRDAPSE and placebo of -2.7 (*p*=0.002), indicating that clinicians perceived a greater worsening of clinical symptoms in patients who were randomized to placebo and discontinued from FIRDAPSE treatment, compared to patients who continued FIRDAPSE in the double-blind period.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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 is supplied as follows:

Child Resistant Blister Pack

- Blister pack containing 10 tablets NDC 69616-211-04
- Carton containing 12 blister packs (120 tablets total) NDC 69616-211-06

Bottles

- 60 tablets NDC 69616-211-08
- 240 tablets NDC 69616-211-03

16.2 Storage and Handling

Store FIRDAPSE tablets at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]. See Dosage and Administration (2.5) for storage instructions for FIRDAPSE prepared suspension.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risk of Seizures

Inform patients that FIRDAPSE can cause seizures, and to notify their healthcare provider if they experience a seizure [see *Warnings and Precautions (5.1)*].

Hypersensitivity

Instruct patients to inform their healthcare provider if they have signs or symptoms of hypersensitivity, and to seek emergency help if symptoms of anaphylaxis occur [see *Warnings and Precautions (5.2)*].

FIRDAPSE 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 [see *Dosage and Administration (2)*]. 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 [see *Dosage and Administration (2.5)*]. 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.

Drug Interactions

Instruct patients to notify their healthcare provider prior to starting any new medication, including over-the-counter drugs [see *Drug Interactions (7)*].

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking FIRDAPSE they should inform their healthcare provider. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to FIRDAPSE during pregnancy and encourage them to enroll if they become pregnant while taking FIRDAPSE [see *Use in Specific Populations (8.1)*].

Storage

Advise patients to store FIRDAPSE at 68°F to 77°F (20°C to 25°C).

Instruct patients and/or caregivers who prepare the 1 mg/mL suspension of FIRDAPSE that it should be prepared daily and refrigerated between doses. The suspension can be stored under refrigeration for up to 24 hours. Instruct the patient and/or caregiver to discard any unused portion of the suspension after 24 hours.

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