



**BioMarin Pharmaceutical Inc.
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RISK MANAGEMENT PLAN

For

Firdapse (amifampridine phosphate)

Date of Report

16 February 2017

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PART I: PRODUCT OVERVIEW

Active substance (INN or common name):	amifampridine phosphate; 3,4-diaminopyridine (3,4-DAP) phosphate
Pharmaco-therapeutic group (ATC Code):	Nervous system; other nervous system drugs; amifampridine (N07XX05)
Name of Marketing Authorisation Holder or Applicant:	BioMarin Europe Limited 10 Bloomsbury Way London UK WC1A 2 SL
Number of medicinal products to which this RMP refers:	One
Product(s) concerned:	Firdapse (amifampridine phosphate)

Data lock point for current RMP

1 January 2016

Version Number

11.0

Date of final sign off

4 October 2016

ADMINISTRATIVE INFORMATION ON THE RMP

PART	MODULE/ANNEX	Date when the module or part was last submitted (final sign off date)	Version number of RMP when last submitted
PART II Safety Specification	SI Epidemiology of the indication and target populations(s)	18 December 2013	4.0
	SII Non-clinical part of the safety specification	16 February 2017	11.0
	SIII Clinical trial exposure	25 September 2015	7.0
	SIV Populations not studied in clinical trials	16 February 2017	11.0
	SV Post-authorisation experience	25 September 2015	7.0
	SVI Additional EU requirements for the safety specification	16 February 2017	11.0
	SVII Identified and potential risks	16 February 2017	11.0
	SVIII Summary of the safety concerns	4 October 2016	10.0
PART III Pharmacovigilance Plan		16 February 2017	11.0
PART IV Plan for post-authorisation efficacy studies		4 October 2016	10.0
PART V Risk Minimisation Measures		4 October 2016	10.0
PART VI Summary of RMP		16 February 2017	11.0
PART VII Annexes	ANNEX 2 Current or proposed SPC/PIL	16 February 2017	11.0
	ANNEX 3 Worldwide marketing status by country	18 December 2013	4.0
	ANNEX 4 Synopsis of clinical trial programme	25 September 2015	7.0
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	18 December 2013	4.0
	ANNEX 6 Protocols for proposed and ongoing studies in Part III	25 September 2015	7.0
	ANNEX 7 Specific adverse event follow-up forms	18 December 2013	4.0

PART	MODULE/ANNEX	Date when the module or part was last submitted (final sign off date)	Version number of RMP when last submitted
	ANNEX 8 Protocols for studies in Part IV	18 December 2013	4.0
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	22 June 2016	9.0
	ANNEX 10 Details of proposed additional risk minimization activities	18 December 2013	4.0
	ANNEX 11 Mock up examples	18 December 2013	4.0
	ANNEX 12 Other supporting data	18 December 2013	4.0

QPPV Name:

Sandra Van der Poel

Signature:

Contact person for this RMP:

E-mail address or telephone:

Proprietary

Overview of Versions

Version number of last agreed RMP:	8.0
Agreed within	Centralized procedure

Invented name(s) in the European Economic Area (EEA)	Firdapse		
Authorisation procedure	Centralised		
Brief description of the product including: chemical class summary of mode of action important information about its composition (eg, origin of active substance of biological, relevant adjuvants or residues for vaccines)	Aminopyridine; amifampridine blocks voltage-dependent potassium channels, thereby prolonging pre-synaptic cell membrane depolarization. Prolonging the action potential enhances the transport of calcium into the nerve ending. The resulting increase in intracellular calcium concentration facilitates exocytosis of acetylcholine-containing vesicles, which in turn enhances neuromuscular transmission.		
Indication(s) in the EEA Current (if applicable) Proposed (if applicable)	Symptomatic treatment of Lambert Eaton Myasthenic Syndrome (LEMS) in adults		
Posology and route of administration in the EEA Current (if applicable) Proposed (if applicable)	FIRDAPSE should be given in divided doses, three or four times a day. The recommended starting dose is 15 mg a day, which can be increased in 5 mg increments every 4 to 5 days, to a maximum of 60 mg per day. In exceptional circumstances, higher doses up to a maximum of 80 mg/day may be of benefit when given with the appropriate safety monitoring. No single dose should exceed 20 mg. Tablets are to be taken with food. For oral use only.		
Pharmaceutical form(s) and strengths Current (if applicable) Proposed (if applicable)	White, round, flat-faced, and scored tablet on one face; each tablet contains amifampridine phosphate equivalent to 10 mg of amifampridine.		
Country and date of first authorisation worldwide	EU	23 December 2009	
Country and date of first launch worldwide	Germany	April 2010	
Country and date of first authorisation in the EEU	EU	23 December 2009	

Is the product subject to additional monitoring in the EU? Yes ☒ No ☐

ABBREVIATIONS AND TERMS

3,4-DAP	3,4-diaminopyridine
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse event
AGEPS	General Agency for Health-Care Equipment and Products
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ATU	Authorization temporaire d'utilisation
BPM	Beats per minute
BPV	BioMarin Pharmacovigilance
CAPA	Corrective Action, Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CMAP	Compound muscle action potential
CSR	Clinical study report
CTD	Clinical trial document
DLP	Data lock point
DSUR	Development Safety Update Report
EMA	European Medicines Agency
ECG	Electrocardiogram
EEG	Electroencephalogram
EU	European Union
EEA QPPV	European Economic Area Qualified Person for Pharmacovigilance
γ GT	Gamma-glutamyl transpeptidase
g	gram
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLT	High level term
HLGT	High level group term
ICSR	Individual case safety report
IQR	Interquartile range
IV	Intravenous
IVIG	Intravenous immunoglobulin
LEMS	Lambert-Eaton Myasthenic Syndrome
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic resonance imaging

MS	Multiple sclerosis
Msec	millisecond
NMJ	Neuromuscular Junction
NAT	N-acetyl transferase
PIL	Patient Information Leaflet
Pgp	P-glycoprotein
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
QTc	Rate corrected QT interval
RMP	Risk Management Plan
SAE	Serious adverse events
SCLC	Small cell lung cancer
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
TBD	To be determined
TdP	Torsades de pointes
TUP	Therapeutic Use Protocol
ULN	Upper limit of normal
US	United States
VC	Vital capacity

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the indication(s) and target population

Indication

SI.1: Epidemiology of the Disease

Incidence and Prevalence:

LEMS is a paraneoplastic syndrome in approx. 40% to 60% of the cases. Small cell lung cancer (SCLC) is by far the most frequent underlying malignancy ([Sanders, 2003, Ann.N.Y.Acad.Sci.](#)); ([Tim, 2000, Neurology](#)). However, only 1-3% of patients with SCLC develop LEMS ([Sanders, 2003, Ann.N.Y.Acad.Sci.](#)). Non-paraneoplastic LEMS is frequently associated with other autoimmune disorders. Phenotypically, both forms appear to be identical ([Newsom-Davis, 2004, Rev.Neurol.\(Paris\)](#)).

Incidence: For paraneoplastic (specifically, SCLC-related) LEMS, an annual incidence of 5 per million has been estimated for the UK ([Newsom-Davis, 2004, Rev.Neurol.\(Paris\)](#)). Based on US cancer statistics.

([Ries, 2007, SEER website](#)) which report an annual incidence of SCLC of 9.4 per 100,000 and the notion that approx. 1-3% of patients with SCLC develop LEMS ([Sanders, 2003, Ann.N.Y.Acad.Sci.](#)), an annual incidence for paraneoplastic LEMS of approx. 1 to 3 cases per million can be assumed. The annual incidence of non-paraneoplastic LEMS has been estimated as being lower than paraneoplastic LEMS, namely <1 per million ([Newsom-Davis, 2004, Rev.Neurol.\(Paris\)](#)).

The EU Committee for Orphan Medicinal Products estimated a prevalence of LEMS of about 1 per 100,000 in the European population. A similar figure has been estimated for the US ([Sanders, 2003, Ann.N.Y.Acad.Sci.](#)). Because of the higher mortality of patients with neoplastic background, the prevalence of paraneoplastic and non-paraneoplastic LEMS might be similar. LEMS represented about 1% of cases with myasthenia in a Dutch study ([Wirtz, 2003, J.Neurol.](#)).

Demographics of the Target Population:

Although there are case reports of diagnosis of LEMS in children, the majority of patients with LEMS are relatively elderly adults, on average 56 years old ([Tim, 2000, Neurology](#)). As SCLC is often associated with history of regular tobacco smoking, LEMS shows a similar but weaker association. LEMS does not appear to have a higher prevalence in either sex ([Sanders, 2003, Ann.N.Y.Acad.Sci.](#)), ([Wirtz, 2003, J.Neurol.](#)).

Risk Factors for the Disease:

None identified.

Treatment Options:

Treatment of patients with LEMS can be classified into 3 main categories, each targeting different aspects of the pathogenesis of the disease: 1) anti-tumor treatment(surgery, radiation, chemotherapy) in paraneoplastic LEMS; 2) immunologic treatments (intravenous immunoglobulin, plasma exchange, prednisone, azathioprine, cyclosporine) to suppress anti-VGCC; and 3) symptomatic treatment (pyridostigmine, amifampridine acting at the neuromuscular junction ([Verschuuren, 2006, Expert.Opin.Pharmacother.](#))).

Mortality and Morbidity and Implications for Public Health:

Mortality is dependent on the pathogenesis of the disease. Morbidities are consistent with the elderly population.

SI.2: Concomitant Medication(S) In the Target Population

Supportive care is most commonly utilized in conjunction with this medicinal product.

SI.3: Important Co-Morbidities Found In the Target Population

The indication of symptomatic treatment of LEMS, given that the majority of LEMS cases are paraneoplastic, implies that many treated individuals will be cancer patients. In the non-paraneoplastic LEMS patients, concurrent autoimmune disorders are present in the majority of patients.

There is no evidence from the published clinical experience with 3,4-DAP, or from clinical trials with Firdapse to date, that the drug affects the course of these co-morbidities. There is also no indication that patients with these diseases are at an increased risk for toxicity.

It may be hypothesized that patients whose underlying disease affects target organs of Firdapse toxicity may be at an increased risk for undesirable effects (e.g., patients with cerebral metastases may be at an elevated seizure risk).

Module SII: Non-Clinical Part of the Safety Specification

Key Safety findings (from non-clinical studies)	Relevance to Human Usage
CNS-related clinical signs including convulsions/Single and repeat-dose toxicity	CNS-related clinical signs including convulsions have been documented in the clinical database. These clinical signs are related to mechanism of action of the parent drug in the brain, N-acetyl transferase polymorphism metabolic status may also affect the C _{max} concentrations of the parent drug.
Developmental toxicity	Developmental studies have been conducted in rats at oral doses, TID up to 75 mg/kg/day amifampridine phosphate (BioMarin Study No. BMN125-013-012) and in rabbits (BioMarin Study No. BMN125-13-015) at oral doses up to 57 mg/kg/day amifampridine phosphate (about 6.4 and 9.7 times the recommended human dose of 60 mg/day based on body surface area, respectively). These studies revealed no evidence of harm to the embryo or fetus due to amifampridine. The peri- and post-natal study in rat (BioMarin Study No. BMN125-13-025) showed a dose-related increase in the percentage of mothers having stillborn pups when treated with ≥ 22.5 mg/kg/day amifampridine phosphate. There was no observed effect on the development of the offspring from treated mothers, including behavioural assessments. Amifampridine was confirmed to be present in the breast milk of treated dams.
Nephrotoxicity	No evidence of nephrotoxicity based on nonclinical data
Hepatotoxicity	No hepatotoxicity observed. In addition within the recommended therapeutic range of amifampridine dosing (20 mg single dose) and the resulting human plasma concentrations, drug-drug interactions related to CYP450 inhibition or induction, or plasma protein binding effects are not likely to occur or be clinically significant

Key Safety findings (from non-clinical studies)	Relevance to Human Usage
Reproductive toxicity	Reproduction studies have been conducted in rats at oral doses, TID up to 75 mg/kg/day amifampridine phosphate (BioMarin Study No. BMN125-13-012). These studies revealed no evidence of impaired fertility, mating or reproduction in rats up to 75 mg/kg/day amifampridine phosphate (about 6.4 and 9.7 times the recommended human dose of 60 mg/day based on body surface area).
Carcinogenicity	Amifampridine has been shown to be negative in a battery of genotoxicity studies (Study Nos. IPL-r-010310, IPL-r-010417, IPL-r-010515, IPL-r-020404, and IPL-r-010417). In a 2-year rat dietary carcinogenicity study, amifampridine caused small but statistically significant dose-related increases in the incidence of Schwannomas in both genders and of endometrial carcinomas in females. The clinical relevance of these results are unknown.
Long-term toxicity	A 13-week repeat-dose toxicity study in rats was conducted (BioMarin Study No. BMN125-10-055). Amifampridine phosphate was tolerated at doses up to 22.5 mg/kg/day. Adverse events were noted based on CNS effects similar to those observed in previous repeat-dose toxicity studies. Collection and analysis of long-term usage data to be an objective of the Pharmacovigilance Plan.
Pharmacokinetics (distribution, protein binding, metabolism, and elimination): No preclinical <i>in vivo</i> data available, but bibliographical data available.	¹⁴ C-Amifampridine is categorized as a low plasma protein binding compound, and pharmacokinetic interactions with highly bound drugs are unlikely. ¹⁴ C-Amifampridine partitions equally into plasma and blood cells. In the rat, amifampridine has about 94% bioavailability. The main metabolite observed in the rat was 3-N-acetylated amifampridine ((N-(4-aminopyridin-3-yl) acetamide). In the rat and dog, the main route of elimination is via the urine. A known human polymorphism of the N-acetyl transferase enzyme can impact the levels of parent drug and the potential for CNS-related clinical signs. Limited bibliographic data and long term limited clinical experience supports current use. Lack of data and the communication relevant to risks based on assumed mechanisms (e.g., with regard to patients with renal impairment) are reflected

Key Safety findings (from non-clinical studies)	Relevance to Human Usage
	in the SPC in Sections 4 and 5.2. Experience in patient subpopulations (e.g., renal impairment) to be a focus of the Pharmacovigilance Plan.
Photosafety: No non-clinical data.	There is no indication of phototoxicity in repeat dose studies in rat or dog. No indication towards phototoxicity from available bibliographic data and clinical experience. 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°C 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. Addressed as missing information in the Pharmacovigilance Plan.
General safety pharmacology Cardiovascular (including potential for QT interval prolongation) Central nervous system Respiratory system	In vitro assessment of amifampridine effects on the inward rectifying voltage gated potassium channel (hERG) were not observed up to concentrations of 30 µM. In vitro assessment of amifampridine effects on rabbit isolated Purkinje fibers up to 100 µM indicated a dose related increased action potential duration when a stimulation frequency of 1 Hz was used as well as in case of bradycardia (0.2 Hz), probably indicating blockade of K⁺ channels (Class III anti-arrhythmic effects). In vivo cardiovascular safety pharmacology was evaluated in telemetry-instrumented dogs given up to 0.50 mg/kg, PO with no significant effects on heart rate or body temperature or QT/QTc interval. Amifampridine shortened the PR interval up to -8% and increased arterial pulse pressure up to +7%. The significance of these results is unknown but does not appear to translate to the human (see QTc study No. QTC-002) There were no amifampridine-related effects on the behavioral Irwin test in rats given up to 40 mg/kg. There were no amifampridine-related effects on respiratory function (tidal volume, respiratory rate, minute volume) after a single dose of amifampridine in rats up to 10 mg/kg. Based on the current knowledge, cardiovascular, respiratory or CNS effects are unlikely at the doses evaluated.

Key Safety findings (from non-clinical studies)	Relevance to Human Usage
Mechanisms for drug interactions	¹⁴C-Amifampridine is categorized as a low plasma protein binding compound, and pharmacokinetic interactions with highly bound drugs are unlikely. The results from an <i>in vitro</i> CYP450 inhibition and induction study indicate that amifampridine does not inhibit or induce the major hepatic CYP450 enzymes. Acetaminophen inhibits NAT2 <i>in-vitro</i> and when co-administered with amifampridine <i>in-vivo</i> may result in increases in amifampridine exposure. Based on limited information available, the potential for drug interactions is unknown. If possible, monitoring and necessary dose adjustment of concomitant medications is advised. Concomitant use of medicinal products with a narrow therapeutic window is contraindicated

No additional non-clinical data are deemed necessary for use in special populations considering the long-term clinical experience.

SII.1: Conclusions on Non-Clinical Data

Safety Concerns	
Important identified risks (confirmed by clinical data);	Seizures
Important potential risks (not refuted by clinical data or which are of unknown significance)	Risk of nerve sheath tumour development (Schwannoma in rats)
Missing information	There is no evidence of phototoxicity in any of the toxicity studies performed to date.

Module SIII: Clinical Trial Exposure**SIII.1: Brief Overview of Development**

The clinical data for Firdapse prior to Marketing Authorisation originated primarily from published clinical trials using 3,4-DAP rather than a classical clinical development program, and one bioequivalence study (DAPSEL) conducted with tablets containing 3,4-DAP phosphate and capsules containing 3,4-DAP free base.

SIII.2: Clinical Trial Exposure**LMS-001****A Phase 1, Randomized, Open-Label, Two-Treatment, Two-Period Crossover Study to Evaluate the Effect of Food on Relative Bioavailability of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Healthy Subjects**

Forty seven healthy subjects were enrolled in this completed study. The age of the subjects enrolled ranged between 19 and 62 years and BMI ranged between 19.4 and 29.5 kg/m². Forty-one of 47 enrolled subjects were white, [REDACTED] subjects and [REDACTED] subject were Black/African American, and 3 subjects were of multiple race ([REDACTED] Iranian + Caucasian, [REDACTED] white + Bangladesh, [REDACTED] white + black).

Extent of Exposure: 28 male and 16 female subjects each received 2 single oral doses of amifampridine phosphate for a total of 40 mg amifampridine per subject. Three of the 47 subjects each received a single oral dose of 20 mg amifampridine before withdrawing from study participation. All 3 subjects who withdrew were male.

FIR-001**A Phase 1, 2-part, Open Label Pharmacokinetic and Safety Study to Evaluate Dose Proportionality and Accumulation of Firdapse (3,4-Diaminopyridine Phosphate) after Single and Multiple Oral Doses in Healthy Volunteers**

A total of 26 healthy male and female subjects were enrolled in the study: 12 in Part 1 (7 males and 5 females), 4 in Part 2 Group 1 (3 males and 1 female), and 10 in Part 2 Group 2 (8 males and 2 females). Overall, the age of the subjects enrolled ranged between 18 and 54 years and BMI ranged between 18.2 and 28.7 kg/m². Twenty-three of 26 enrolled subjects were white. [REDACTED] subject in Part 1 was American Indian or Alaska Native, [REDACTED] subject in Part 1 was of multiple race (white + black), and [REDACTED] subject of Part 2 Group 2 was also of multiple race (white + Asian).

Extent of Exposure: All 12 subjects of Part 1 received a total of 65 mg amifampridine, all 4 subjects of Part 2 Group 1 received a total of 80 mg amifampridine and all 10 subjects of Part 2 Group 2 received a total of 260 mg amifampridine.

LMS-002**A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Randomized Discontinuation Study Followed by an Open-Label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with Lambert-Eaton Myasthenic Syndrome (LEMS)**

LMS-002 is an ongoing study. Fifty-four patients with Lambert Eaton Myasthenic Syndrome were enrolled in Part 1 (open-label run in) of the study. Eighteen (34%) were male and 35 (66%) were female; 48 were white, 4 were Hispanic/Latino, 1 Black or African American, and 1 not reported. One patient discontinued the study following 1 dose of amifampridine. Thirty-eight of the 54 patients who had enrolled in Part 1 entered Parts 2 and 3 of the study (double-blind phase with a mean age of 51.5 years (range 21 to 88 years). Twenty-three (60.5%) patients were female, and the majority of patients were not Hispanic or Latino (34 patients [89.5%]). Thirty-four (89.5%) patients were white. Thirty-eight patients continued on Part 4 of the study (open-label long term safety, ongoing). Two additional patients were enrolled and were allowed to move directly to Part 4.

Extent of Exposure: The dose of Firdapse is 30 to 80 mg/day divided into 3 or 4 doses with a maximum of 20 mg at any single oral administration. The dose was individually determined by the investigator and titrated from 30 mg/day to an optimal dose level, not to exceed 80 mg/day, based on the patients' previous history with amifampridine (if any) and observed optimal neuromuscular benefit.

QTC-002**A Phase 1, Double-Blind, Randomized, Crossover Study to Define the ECG Effects of Amifampridine Phosphate Using a Therapeutic and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women Who Are Slow Acetylators: A Thorough QT Study**

In Part 1, of the 8 subjects studied, 5 were female and 3 were male. All 8 subjects were white. As per the inclusion criteria, all subjects were aged between 18 and 55 years, with a BMI between 18 and 30 kg/m².

In Part 2, of the 52 subjects studied, 38 were male and 14 were female. Overall 46 subjects were white (██████████), 3 subjects were Asian (██████████), and 2 subjects were Black or African American (██████████). One subject was identified as 'Other'. As per the inclusion criteria, all subjects were aged between 18 and 55 years, with a BMI between 18 and 30 kg/m².

Extent of exposure: In Part 1, a total of 6 subjects (4 female and 2 male) were exposed to single oral doses of 30 mg, 60 mg, 70 mg amifampridine phosphate, and 80 mg amifampridine phosphate, giving a total exposure of 240 mg amifampridine phosphate

per subject. Two subjects (1 male and 1 female) were exposed to 4 single oral doses of placebo.

In Part 2, a total of 51 subjects (37 male and 14 female) were exposed to single oral doses of 30 mg amifampridine phosphate, 60 mg amifampridine phosphate, 400 mg moxifloxacin, and placebo. One subject (subject [REDACTED]) was exposed to a single oral dose of 30 mg amifampridine phosphate.

REN-002

A Multi-Center, Open-Label Phase I Study to Investigate the Effect of Different Degrees of Renal Impairment on the Single-Dose Pharmacokinetics of Amifampridine Administered as a Phosphate Salt in Patients with Renal Impairment Compared to Subjects with Normal Renal Function

The ages of the 16 subjects having an acetylation status of slow acetylation ranged between 40 and 69 years, while the age of the 16 subjects classified as rapid acetylators ranged between 39 and 69 years. Gender distribution in both acetylation groups was balanced across all renal function groups (normal, mild impairment, moderate impairment, severe impairment). All 32 subjects were white.

Extent of Exposure: Every subject enrolled in the study received a single dose of amifampridine phosphate (10 mg).

Module SIV: Populations Not Studied In Clinical Trials**SIV.1: Limitations of ADR Detection Common to Clinical Trial Development Programmes**

Ability To Detect Adverse Reactions	Limitation Of Trial Programme	Discussion Of Implications For Target Population
Which are rare	Being an orphan drug used for a rare indication exposure to drug remains low.	ADRs with low frequency may not have been detected because of the limited sample size
Due to prolonged exposure	Trials included finite treatment period on healthy volunteers and limited number of patients in clinical trials	Ongoing study and registry to follow patients for long-term effects (LEMS-001, and LMS 002)
Due to cumulative effects	Trials included finite treatment period on healthy volunteers and limited number of patients in clinical trials	Ongoing study and registry to follow patients for cumulative effects (LEMS-001, and LMS 002)
Which have a long latency	Trials included finite treatment period on healthy volunteers and limited number of patients in clinical trials	Ongoing study and registry to follow patients long term for events with long latency (LMS-002, and LEMS 001)

SIV.2: Effect of Exclusion Criteria in the Clinical Trial Development Plan

Exclusion Criteria Which Will Remain As Contraindications	
Criteria	Implications for target population
History of seizure	Patients with epilepsy
History of Asthma	Patients with uncontrolled asthma
Rate corrected QT interval (QTc) ≥ 430 msec (Bazett's formula)	Patients concomitantly on medicinal products with a known potential to cause QTc prolongation and in patients with congenital QT syndrome

Exclusion Criteria Which Are NOT Proposed To Remain As Contraindications		
Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Age < 18 or > 45 years	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Female gender	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Body mass index < 19 or > 28 kg/m ²	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Abdominal clinical examination	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Biological parameters not within normal ranges of the local laboratory (blood count, platelets, blood and urine electrolytes, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyl transpeptidase (γGT), and total bilirubin)	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Positive serology results for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV)	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Any current disease	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
History of drug allergy	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
History of psychiatric disorders	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Any drug intake within the 15 days before study initiation	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Heavy smoker (more than 10 cigarettes/day)	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Alcohol abuse (more than 50 grams (g) per day)	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting

Exclusion Criteria Which Are NOT Proposed To Remain As Contraindications		
17. Blood transfusion or donation in the past 3-months	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting
Subject not available for the total study period	Recognized healthy volunteer Pharmacokinetic study exclusion criteria	Not a relevant concern for product in non-study setting

SIV.3: Limitations in Respect to Populations Typically Under-Represented In Clinical Trial Development Programmes

The Clinical Summary (Firdapse Marketing Authorization Application (MAA) Clinical Trial Document (CTD) module 2.7 Clinical Summary) for Firdapse reflects the pre-Marketing Authorisation exposure of approximately 2,300 patients to 3,4-DAP, of whom between 284 and 324 patients suffered from LEMS. A more precise figure cannot be given because the indication for treatment with 3,4-DAP is not known for all patients treated under the French TUP.

In patients with LEMS, there were three placebo-controlled trials and one active-controlled crossover trial involving 39 patients; all patients received 3,4-DAP and control during these trials. Additionally, there was one placebo-controlled parallel group trial involving 12 patients randomised to 3,4-DAP and 14 patients randomised to placebo.

Numbers of patients exposed to treatment in the uncontrolled studies and the case reports were counted together. Approximately 150 patients with LEMS were reported with mention of treatment with 3,4-DAP. The estimate aimed to avoid double-counting of patients reported in different papers. Nearly one-half of these patients (53 patients) were mentioned in one report alone ([Tim, 2000, Neurology](#)), which described patients with LEMS rather than specific treatment with 3,4-DAP.

Since 1996, approximately 90 patients with LEMS were treated in France with 3,4-DAP provided by the General Agency for Health-Care Equipment and Products (AGEPS). In addition, approximately 1,170 patients were treated with 3,4-DAP provided by AGEPS for other indications. Some pharmacovigilance reports are available from this group of patients.

In addition, from December 2006 to December 2008, 114 patients were treated with 3,4-DAP under the TUP in France. Of these patients, at least 39 suffered from LEMS (PSUR from 01 January 2008 to 31 December 2008).

Most patients with LEMS were treated over the long-term (weeks to months), while some received the drug for several years. A number of reports merely mentioned treatment with 3,4-DAP, without providing further details sufficient to form a judgment on safety and tolerability.

3,4-DAP has also been investigated in other indications. Respective safety data including relevant background information are presented in the Clinical Summary (Firdapse MAA CTD module 2.7 Clinical Summary). There were eight relevant studies with 3,4-DAP for indications other than LEMS (among them 5 placebo-controlled cross over studies) involving a total of 156 patients and a large retrospective observational study of 669 patients with multiple sclerosis (MS) treated with 3,4-DAP between 01 November 1998 and 31 December 2003.

In addition, in an open prospective trial, 16 patients (aged 7 to 47 years) with congenital myasthenia received doses of 3,4-DAP between 5 to 20 mg three or four times daily (Palace, 1991, [J.Neurol.Neurosurg.Psychiatry](#)).

Dosing ranged from 20 mg to 100 mg per day per os, with at least 10 patients with LEMS receiving 100 mg/day. Three of the 5 placebo or active controlled trials included an open-label follow-up period of at least 3 months. Follow-up for several months was reported from most observational studies and case reports; some patients received the drug for several years.

The very low prevalence and the clinical context of LEMS (frequently a paraneoplastic syndrome in patients with limited life expectancy), as well as the fact that 3,4-DAP is recommended as symptomatic therapy in treatment guidelines based on the already available clinical trial data, significantly impede clinical trial options and need to be taken into account when judging the clinical trial exposure to 3,4-DAP.

Children

Only two cases of children were reported and published. The very low incidence of LEMS in children limits the option to collect controlled data in this population. The lack of information in this population is pointed out in the SPC in Sections [4.2](#) and [5.2](#).

Elderly

Many of the patients treated with 3,4-DAP for LEMS were elderly. No special safety concerns arose from the clinical experience with 3,4-DAP in this population.

Pregnant or Lactating Women

Pregnant women were excluded from those trials for which the exclusion criteria are known. Case reports on foetal exposure with 3,4-DAP have been reported in the literature (Peluso-Pellicer, 2006, [Ann.Pharmacother.](#)); (Vinke, 2007, [Geburtschilfe Frauenheilkd](#)); (Reuner, 2008, [J.Neurol.](#)); (Schneider-Gold, 2006, [J.Neurol.](#)); (Bayrak, 2010, [Int.J.Neurosci.](#)); (Lecky BRF, 2006, [J Neurol Neurosurg Psychiatry](#)). No adequate clinical data on exposed pregnancies are available for amifampridine. Based on available non-clinical data (which showed no effect on embryo-fetal viability and development in rabbits, but showed an increase in the number of mothers delivering still-born offspring in rats), Firdapse should not be used during pregnancy. Women of child bearing potential must take effective contraceptive measures when being treated with 3,4-DAP.

It is not known whether 3,4-DAP is excreted into the breast milk in humans. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Firdapse therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

The relevant information is included in Section 4.6 of the SPC.

Currently, there is little evidence that 3,4-DAP is being routinely prescribed in pregnancy and therefore the warnings in the labelling should suffice for any pharmacovigilance activity.

Patients with Relevant Co-Morbidity

Patients with renal or hepatic disease were excluded from those clinical trials for which the exclusion criteria are known. There have been no clinical pharmacology studies in patients with hepatic disease, and the lack of clinical data from patients with hepatic disease is considered missing information that will be adequately communicated and is included in Sections 4.2, 4.4, and 5.3 of the SPC. 3,4-DAP is metabolised by N-acetylation and urinary excretion of the compound and its N-acetylated metabolite(s) is the primary elimination route (LMS-001 Clinical Study Report (CSR)). The use of Firdapse in patients with renal and hepatic impairment will require special precaution for use as is noted in the SPC.

In a PK study of subjects with varying degrees of renal impairment compared to subjects with normal renal function, subjects received a single 10 mg dose of amifampridine. Exposure by AUC was up to 3-fold higher in subjects with severe renal impairment; therefore, amifampridine should be dosed to effect with regard to both frequency of administration and dose level. No adverse events were assessed as related to amifampridine and no serious adverse events were reported. The NAT2 acetylation status was shown to be a greater contributor than renal function for the PK of amifampridine. This clinical information is included in Sections 4.2, 4.4, and 5.3 of the SPC.

Patients with convulsive disorders or seizure history were excluded from those clinical trials for which the exclusion criteria are known, due to the established dose dependent pro-convulsive properties of 3,4-DAP. The SPC for Firdapse therefore includes a contraindication for patients with epilepsy, communicates the pro-convulsive properties of 3,4-DAP, and cautions the use of Firdapse in patients with a history of neurological disease and patients concurrently taking other seizure threshold lowering drugs.

No differences were reported with regard to patients with or without carcinoma. Data from a 2-year non-clinical carcinogenicity study is provided in [Module SII](#).

Patients with Disease Severity Different From That Studied In Clinical Trials

The severity of LEMS reported from patients enrolled in the published clinical trials covered a broad range as evaluated by the quantitative myasthenia gravis score, a

neurologic disability score, and/or the compound muscle action potential. Most patients benefited from 3,4-DAP.

Sub-Populations with Genetic Polymorphisms

Due to the metabolism of 3,4 –DAP by a single polymorphic N-acetyl transferase pathway, administration of Firdapse results in variable exposure for the same dose depending on an individual's NAT2 genotype and overall acetylation phenotype (clinical study FIR-001). A slow acetylator phenotype will have a higher exposure to 3,4 DAP than a rapid acetylator at the same dose level. A slow acetylator may have a higher potential for AEs related to enhanced 3,4 –DAP exposure; however, this risk is considered to be well managed by the currently recommended physician implemented dose titration approach (present in the SPC label).

FIR-001, a single and multiple-dose pharmacokinetics (PK) study in healthy volunteers was initiated on 18 May 2011 and the final CSR was submitted to European Medicines Agency (EMA) on 23 February 2012. FIR-001 indicated that slow acetylators were shown to have greater plasma drug levels and more frequent AEs compared to fast acetylators.

Patients of Different Ethnic Origins

No data available.

SIV.4: Conclusions on the Populations Not Studied and Other Limitations of the Clinical Trial Development Programme

Missing Information

Safety Concerns Due To Limitations Of The Clinical Trial Programme	Outstanding Concern?
Lack of information on use in patients with hepatic disease	Yes
Lack of clinical information in paediatric use	Yes
Lack of information on use during pregnancy and lactation	Yes
Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants)	Yes

Module SV: Post-Authorisation Experience**SV.1: Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons**

No regulatory actions were taken for safety reasons since the prior RMP.

SV1.1: Detailed Description of Action Taken Since Last Update to this Module

Not applicable.

SV1.2: Cumulative List

Not applicable

No significant actions related to safety have been taken during the reporting period, related to either Firdapse investigational uses or marketing experience, by BioMarin, regulatory authorities, data monitoring committees, or ethics committees that had:

- A significant influence on the benefit-risk profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

SV.2: Non-Study Post-Authorisation Exposure

Firdapse received Marketing Authorisation in the EU on 23 December 2009, and was launched in April 2010. During the most recent PBRER period (24 December 2013 to 23 December 2014), global marketed patient exposure was estimated to be approximately 412 patients, representing a 28.8% increase in global marketed patient exposure compared to the prior PSUR period (24 December 2012 to 23 December 2013).

In early December 2006, the distribution of 3,4-DAP 10 mg tablets (as phosphate) was authorised on a named patient basis (Authorisation temporaire d'utilisation (ATU) Program) in France by the AFSSAPs as part of a Therapeutic Use Protocol (TUP). The TUP included quarterly patient visits with completion of a dedicated form to collect renal and hepatic parameters, together with any safety data (serious or non-serious AEs, treatment discontinuation, and pregnancy). From 01 December 2006 to 31 December 2008, 114 patients were treated with 3,4-DAP 10 mg tablets, including at least 39 patients with LEMS (indication was documented for 72 of the 114 patients). During the period from 01 January 2008 to 31 December 2008, the mean dose of Firdapse received per day by patients within the ATU was 28.4 mg (range, 10-80 mg and median dose 30 mg/day), based on 39 of 43 patients in the program during this period for whom dosage was reported. The ATU for 3,4-DAP phosphate in France is now closed.

SV2.1: Method used to Calculate Exposure

Exposure in the commercial setting is estimated by using sales figures and dosing data from the LEMS Registry which estimates the mean dose of treatment per patient per day.

Specific patient numbers are not tracked routinely because of patient turnover, sporadic usage patterns in some patients, and data protection concerns.

SV2.2: Exposure

Table 1: By Country

Country	Estimated Patients on Firdapse as of 1 January 2016
EU Countries	
Netherlands	
Austria	
France	
Denmark	
Slovakia	
Malta	
Sweden	
Germany	
Greece	
Italy	
Spain	
Portugal	
Poland	
United Kingdom	
Non-EU Countries	
Israel	
Switzerland	
Norway	

SV.3: Post-Authorisation Use in Populations Not Studied in Clinical Trials

None.

SV.4: Post-Authorisation Off-Label Use

None.

SV.5: Epidemiological Study Exposure

Study Title and Study Type (eg, cohort or case/control)	Objectives	Population Studied (data source and country)	Duration (study period)	Number of Persons (in each group of cases and controls) and Person-Time (if applicable)
(Eymard, 2006, Clinical Study Report, AGEPS)	Retrospective descriptive cohort	Patients with LEMS treated with 3,4-DAP (10-50 mg/day)	1996-2004	7; median treatment duration 60 months.
(Centre Hospitalier Regional de Rennes 2006)	Retrospective descriptive cohort	Patients with multiple sclerosis (N=665), LEMS (N=3) or Steinert's disease (N=1), treated with 3,4-DAP (20-80 mg/day)	01 November 1998 – 31 December 2003	669; median treatment duration 2 months.

Module SVI: Additional EU Requirements for the Safety Specification**SVI.1: Potential for Harm from Overdose**

There is no unusually increased risk of overdose during treatment with Firdapse if the drug is carefully titrated as recommended in the SPC. Based on non-clinical data and three clinical cases reported, symptoms of overdose can be expected to include general weakness combined with diffuse paraesthesia, headache, dizziness, dyspnoea, nausea, vomiting, convulsion, and cardiac rhythm disorders.

SVI.2: Potential for Transmission of Infectious Agents

Firdapse does not contain any animal or human derived materials. No risk for transmission of infectious agents is foreseen.

SVI.3: Potential for Misuse for Illegal Purposes

Firdapse has no known potential for misuse for illegal purposes.

SVI.4: Potential for Medication Errors

The invented name Firdapse received acceptance at the Name Review Group Committee, and subsequently by the EMA (variation no. EMA/H/C/001032/LA/001, 28 January 2010) and is therefore deemed acceptable for use.

Firdapse is only available in a single strength, 10 mg tablet. Detailed instructions on the posology for Firdapse are provided in the PIL in appropriate language for maximum readability to encourage patient compliance, and in the SPC for the prescribing physician. The SPC for Firdapse recommends an initial starting dose of 15 mg, titration of treatment in 5mg increments every 4 to 5 days to a maximum of 60 mg per day. In exceptional circumstances higher doses up to a maximum of 80 mg/day may be of benefit when given with the appropriate safety monitoring. Titration of treatment usually necessitates frequent contact between the prescribing physician and the patient. This should also serve to reinforce patient compliance and allow medication errors to be avoided or detected early, reducing any risk to patients from potential medication errors.

SVI.4.1: Description of Medication Errors During the Clinical Trial Programme

None reported.

SVI.4.2: Preventive Measures for the Final Product(s) Being Marketed

The risk of dosing or administration errors is lowered by labelling (SPC and PIL), and the product should only be started under the supervision of a doctor experienced in treating LEMS.

The European Commission initially granted a marketing authorisation valid throughout the EU for Zenas on 23 December 2009. The invented name was reviewed during the November 2009 NRG Meeting. The positive check by EMEA on the acceptability of the

new name was finalized at the December 2009 CHMP Meeting. The name of the medicine was changed to Firdapse on 28 January 2010.

SVI.4.3: Effect of device failure

Not applicable.

SVI.4.4: Reports of Medication Errors with the Marketed Product(s)

Product Name(s)				
Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
Medication error (administered with drug that is contraindicated in the SPC)	1 (case [REDACTED])	Patient had pre-existing arrhythmias requiring treatment with amiodarone. Patient was then started with amifampridine phosphate. Although no adverse events reported, reporter called in to enquire and report this as he had read the contraindication associated with use of the two drugs in the SPC.	SPC includes adequate information about contraindication associated with use of drugs that cause QT prolongation	No further action required since reporter had read and understood contraindication associated with use of amifampridine phosphate and drugs that prolong QT interval.

SVI.5: Potential for Off-Label Use

There is published documentation of experimental or compassionate use of 3,4-DAP in a number of clinical conditions other than LEMS, for example symptomatic therapy of MS fatigue. No data are available on the extent of such usage outside of published clinical trials.

SVI.6: Specific Paediatric Issues

SVI.6.1: Issues Identified In Paediatric Investigation Plans

Not applicable

SVI.6.2: Potential for Paediatric Off-Label Use

LEMS is primarily a disease of adults and the elderly. However, rare cases have been reported of LEMS diagnosis in children, and off-label paediatric use of Firdapse cannot be ruled out in isolated cases. No specific risk has been identified as associated with paediatric use; however, the SPC communicates lack of clinical data in this population (Section 4.2 and Section 5.2 of the SPC).

SVI.7: Conclusions

Safety Concerns From This Module (to be carried through to Part II, Module SVIII)	
None	

Module SVII: Identified and Potential Risks (Non-ATMP version)

SVII.1: Newly Identified Safety Concerns (since this module was last submitted)

No new safety concerns have been identified since the EU RMP was last submitted.

SVII.2: Recent Study Reports with Implications for Safety Concerns

None.

SVII.3: Details Of Important Identified and Potential Risks from Clinical Development and Post-Authorisation Experience (including newly identified)

Seizures	
Frequency with 95% CI	Frequency is not available for the LEMS population.
Seriousness/outcomes	N/A
Severity and nature of risk	No data on seriousness or severity available. Generally, seizure is a serious condition. Outcome, where reported, was favourable. Where specified, generalised convulsion/grand mal seizure was reported.
Background incidence/prevalence	The incidence of seizure of any cause has been estimated at 44/100,000 person-years; incidence was higher for males than for females (49 and 41 per 100,000 person-years, respectively) (Hauser, 1993, Epilepsia). The lifetime prevalence of epilepsy or seizure disorders has been estimated at 2.9% for US adults aged 18 years or older (Kobau, 2006, Epilepsia). Mortality varies depending on the underlying cause. Emotional stress, sleep deprivation, tiredness, and fever are the most frequently reported seizure precipitants in epilepsy patients (Nakken, 2005, Epilepsy Behav.); (Cull, 1996, Seizure.); (Frucht, 2000, Epilepsia); (Spatt, 1998, Seizure.).
Risk groups or risk factors	The available data do not allow for formal subgroup analysis, however, known risk factors for seizures were present in most patients (MS, toxic theophylline levels, and known epilepsy). In general, patients with central nervous system disorders (e.g., cerebral metastases) or other risk factors which may predispose the patients to seizures or lower the seizure threshold can be assumed to be at increased risk.
Potential mechanisms	A dose-dependent pro-convulsive effect is likely based on animal data. 3,4-DAP passes the blood brain barrier but with tissue levels lower than those observed in plasma. It can be hypothesised that inhibition of K ⁺ channels may affect cerebral function directly or indirectly through altered release of neurotransmitters, thus lowering the seizure threshold.
Preventability	Contraindication of patients with a known seizure disorder and conservative use in other risk patients can be assumed to be suitable measures to minimise the incidence of seizures.
Impact on individual patient	Low; given the fact that seizure disorder are a contraindication.
Potential public health impact of safety concern	Seizure during treatment of patients without risk factors within the recommended dose range appears to be rare and manageable; thus, the potential public health impact is considered to be low.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	MedDRA (Medical Dictionary for Regulatory Activities) SMQ (Standardized MedDRA Queries): Convulsions (broad)

Food/Drug Interaction	
Frequency with 95% CI	N/A
Seriousness/outcomes	Fasting when taking Firdapse may affect the rate and extent of drug absorption. In addition, gastrointestinal side effects may occur more commonly.
Severity and nature of risk	No data on seriousness or severity available.
Background incidence/prevalence	N/A
Risk groups or risk factors	The available data do not allow for formal subgroup analysis.
Potential mechanisms	The rate and extent of absorption of Firdapse is influenced by food. There was a decrease in C_{max} and AUC, and a longer T_{max} when Firdapse was given with food as compared to without food.
Preventability	The SPC (Sections 4.2 and 5.2) contains guidance that Firdapse is to be taken with food.
Impact on individual patient	Low. No events of food-drug interaction have been reported from clinical development or post-authorisation experience.
Potential public health impact of safety concern	Low
Evidence source	Study LMS-001: Phase 1 food effect study in Healthy Volunteers
MedDRA terms	None

Movement Disorders	
Frequency with 95% CI	Not available for LEMS patients
Seriousness/outcomes	N/A
Severity and nature of risk	Limited information available on seriousness, severity, and outcome. The patient with chorea reportedly remained clinically stable for at least 3 years upon reintroduction of 3,4-DAP.
Background incidence/prevalence	This topic was tentatively identified as a potential risk for consideration in the pharmacovigilance plan based on 2 distinct case reports of chorea and an "Extrapyramidal myasthenic syndrome". A distinct clinical entity for investigation or surveillance has not yet been defined. Meaningful epidemiological data therefore cannot be provided.
Risk groups or risk factors	The available data do not allow for risk group analysis.
Potential mechanisms	Unknown. 3,4-DAP passes the blood brain barrier but with tissue levels lower than those observed in plasma. It can be hypothesised that inhibition of K ⁺ channels may affect cerebral function directly or indirectly through altered release of neurotransmitters.
Preventability	No information available.
Impact on individual patient	Theoretically variable dependent on severity and seriousness of specific disorder.
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Movement disorders (MedDRA SMQ: Extrapyramidal syndrome (broad))

Cardiac Toxicity Including QTc Prolongation	
Frequency with 95% CI	Not available for LEMS patients
Seriousness/outcomes	Limited information available on seriousness, severity, and outcome.
Severity and nature of risk	Clinically non-serious palpitations and rhythm disorders comprise the majority of cases
Background incidence/prevalence	QTc prolongation Incidence, prevalence, and mortality depend strongly on cause and extent of QTc prolongation, and the clinical context. Causes include congenital long QT syndrome, hypokalaemia, hypocalcaemia, and numerous drugs such as antiarrhythmics class IA and III, certain neuroleptics, tricyclic antidepressive agents, certain antimicrobials, some antihistaminics, and other drugs. Congenital long QT syndrome has a prevalence of approx. 1 per 10,000 persons (Wehrens, 2002, Ann.Intern.Med.); mortality ranges from 0.9% to 2.6% per year for patients with known long QT syndrome (Booker, 2003, Br.J.Anaesth.). Acquired TdP: The incidence of TdP (excluding TdP associated with ischaemic events such as acute myocardial infarction or unstable angina pectoris) has been reported at 4 per 100,000 per year, and of drug-induced TdP at 3.1 per 100,000 per year (Darpo B, 2001, Eur Heart J). Ventricular tachyarrhythmia: Incidence of VT (excluding episodes associated with ischaemic events such as acute myocardial infarction or unstable angina pectoris) is 15 per 100,000 person-years (Darpo B, 2001, Eur Heart J).
Risk groups or risk factors	The available data do not allow for risk group analysis.
Potential mechanisms	Inhibition of K ⁺ channels may affect cardiac function directly or indirectly through altered release of neurotransmitters. 3,4-DAP was inactive in hERG assay and also inactive at clinically relevant concentrations in the rabbit Purkinje model. Negative hERG assay at up to maximum concentration tested at 30 µM 3,4-DAP.
Preventability	No information available.
Impact on individual patient	Non serious to serious including fatal outcome depending on clinical setting. Based on results of QTC-002 study, no subjects developed new clinically relevant ECG morphological changes following administration of amifampridine phosphate. Data do not support any significant effect of amifampridine on cardiac repolarization.
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Cardiac toxicity including QTc prolongation (MedDRA High Level Group Term HLGTs: Cardiac disorder signs and symptoms, Coronary artery disorders; High Level Term (HLT): ECG investigations; SMQ: Cardiac arrhythmias (incl. sub-SMQs) (broad))

Peripheral Vascular Disorders/Raynaud's Phenomenon	
Frequency with 95% CI	Not available for LEMS patients
Seriousness/outcomes	No data available on seriousness and severity
Severity and nature of risk	
Background incidence/prevalence	Raynaud's disease: The incidence of Raynaud's disease was reported from a cohort with a mean age of 53.5 years at 2.2% in women and 1.5% in men over an observational period of 7 years. Prevalence was reported at 10.9% in women and 7.8% in men (Suter, 2005, Arthritis Rheum.). The prevalence of Raynaud's disease was reported at 5.0% in Charleston, USA (women 5.7%, men 4.3%) and 16.8% in Tarentaise, France (women 20.1%, men 13.5%) (Maricq, 1993, J Rheumatol.). Vasospastic symptoms of Raynaud's disease are frequently transient and rarely interfere with daily activities (Suter, 2005, Arthritis Rheum.).
Risk groups or risk factors	The available data do not allow for risk group analysis.
Potential mechanisms	Peripheral vasoconstriction has been reported from animal and in vitro studies. It can be hypothesised that inhibition of K ⁺ channels may induce vascular contraction directly or indirectly through altered release of neurotransmitters.
Preventability	No information available.
Impact on individual patient	Non serious to serious dependent on clinical presentation.
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Peripheral vascular disorders/Raynaud's phenomenon (MedDRA HLG1: Arteriosclerosis, stenosis, vascular insufficiency and necrosis)

Respiratory Disorders including Bronchospasm	
Frequency with 95% CI	Not available for LEMS patients
Seriousness/outcomes	Non-serious to serious depending on clinical presentation and co-morbidities
Severity and nature of risk	Limited information available.
Background incidence/prevalence	Asthma: Pooled estimate from major population studies of the adult incidence of asthma was 4.6 per 1,000 person-years in women and 3.6 per 1,000 person-years in men (Eagan, 2005, Int.J Tuberc.Lung Dis.). 10-year cumulative incidence in adults (mean age, 49 years), Northern Sweden, 1996: 6.9%; Prevalence ~10% (Hedlund, 2006, Eur Respir.J.). Annual incidence, USA 1996: 6 per 1,000 (Rudd, 2007, J.Asthma). On univariate analysis, asthma increased the relative risk (RR) of death by 1.48 (95% CI 1.29-1.69) (Vandentorren, 2003, Eur Respir.J.).
Risk groups or risk factors	The available data do not allow for risk group analysis. It may be hypothesised that patients with underlying respiratory disease, especially asthma, may be at increased risk for clinically relevant respiratory reactions (Sanders, 1995, Ann.Neurol.) (Sanders, 1998, Ann.N.Y.Acad.Sci.).
Potential mechanisms	No data available. Direct bronchoconstriction due to K ⁺ channel inhibition, or a cholinergic bronchial effect of 3,4-DAP can be hypothesized.
Preventability	No information available.
Impact on individual patient	Low as bronchospasm is amenable to medical treatment
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Respiratory disorders incl. bronchospasm (MedDRA HLGT: Respiratory disorders NEC; SMQ: Asthma/bronchospasm (broad))

Hepatotoxicity	
Frequency with 95% CI	Not available for LEMS patients
Seriousness/outcomes	None reported in clinical studies or post marketing setting
Severity and nature of risk	Limited information available.
Background incidence/prevalence	This topic was tentatively identified as a potential risk for consideration in the Pharmacovigilance Plan based isolated case reports. A distinct clinical entity for investigation or surveillance has not yet been defined. Hepatic disorders in general are very common and may have numerous causes. Mortality is strongly dependent on type, nature, and severity of the disorder. In a US survey (NHANES 1999-2002), the prevalences of elevated ALT, AST, or either ALT or AST were 8.9%, 4.9%, and 9.8%, respectively, in the entire population and 7.3%, 3.6%, and 8.1 %, respectively, after excluding participants who tested positive for HCV antibody or reported excessive alcohol consumption. Strong predictors of elevated ALT activity included increasing waist circumference and body mass index, alcohol consumption, male sex, Mexican American ethnicity, decreasing age, and presence of HCV antibody (Ioannou, 2006, Am.J Gastroenterol.).
Risk groups or risk factors	The available data do not allow for risk group analysis. The report of hepatitis was reportedly confounded by concurrent use of at least one other drug (mitoxantrone).
Potential mechanisms	No data available. Liver enzyme elevations were observed in a rat study at the highest dose (75 mg/kg) (Trial 266/013).
Preventability	No data available.
Impact on individual patient	Variable dependent on clinical presentation and co-morbidities
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Hepatotoxicity (MedDRA SMQ: Drug related hepatic disorders - comprehensive search (broad))

Serious Gastrointestinal Conditions	
Frequency with 95% CI	Not available in LEMS population
Seriousness/outcomes	Low as no serious GI conditions reported to date in clinical studies or post marketing setting
Severity and nature of risk	Unspecific and presumably non-serious gastrointestinal symptoms such as abdominal pain, nausea, diarrhoea, and epigastralgia were commonly reported from several studies.
Background incidence/prevalence	This topic was tentatively identified as a potential risk based on theoretical considerations and reports of non-serious gastrointestinal disease. A distinct clinical entity for investigation or surveillance has not yet been defined. Detailed epidemiological data therefore cannot be provided. The pooled incidence rate from 12 epidemiological studies among non-users of prescription NSAIDs for serious upper gastrointestinal disorders has been reported at 1 per 1,000 person-years: Perforations alone, 0.1 (95% CI: 0.04-0.23); bleeding lesions alone, 0.8 (0.58-0.68); bleeding or perforated lesions, 0.9 (0.66-1.27); serious gastrointestinal ulcer (complicated or without bleeding), 1.0 (0.83-1.15). Rates increased with age and were approximately twice as high in men as in women (Hernandez-Diaz, 2002, J Clin.Epidemiol.). Incidence of gastrointestinal bleeding, 90 per 100,000; common sources: peptic ulcer (51%), varices (11%), oesophagitis (10%), and erosions (5%). Most haemorrhages stop bleeding spontaneously (82%), whereas 18% present with major bleeding (Wara, 1987, Scand.J Gastroenterol.Suppl.).
Risk groups or risk factors	No data available.
Potential mechanisms	No data available. Cholinergic and/or vascular effects on gastrointestinal mucosa can be hypothesised. No evidence to date that this could result in serious gastrointestinal pathology.
Preventability	No data available.
Impact on individual patient	Low based on present data
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Published clinical trials, non-clinical studies (Firdapse MAA CTD module 2.4 Non-Clinical Overview and 2.5 Clinical Overview).
MedDRA terms	Serious gastrointestinal conditions (MedDRA HLGTs: Gastrointestinal haemorrhages NEC; Gastrointestinal inflammatory conditions; Gastrointestinal ulceration and perforation)

Risk of Nerve Sheath Tumour Development (Schwannoma in rats)	
Frequency with 95% CI	Not available in LEMS population
Seriousness/outcomes	Low, as no reports of Schwannoma have been received to date in clinical studies or the post-marketing setting.
Severity and nature of risk	Unspecific, as some events reported in rats were benign; no events have been reported in humans.
Background incidence/prevalence	This topic was identified as a potential risk for consideration in the Pharmacovigilance Plan based animal data. Malignant Schwannoma is listed as rare (<200,000 in US population), peripheral nerve tumors are uncommon. A distinct clinical entity for investigation or surveillance has not yet been defined.
Risk groups or risk factors	No data available.
Potential mechanisms	No data available.
Preventability	No data available.
Impact on individual patient	Low based on present data.
Potential public health impact of safety concern	Unknown due to scarcity of data on frequency, causality, and outcome.
Evidence source	Non-clinical 2-year rat dietary carcinogenicity study (BMN125-13-026)
MedDRA terms	Schwannoma (MedDRA HLGT: Nervous system neoplasms malignant and unspecified NEC)

SVII.4: Identified and Potential Interactions

Overview of Potential for Interactions

Administration of Firdapse with food may reduce bioavailability, leading to reduced efficacy. Prior to marketing authorisation, the effect of food on Firdapse bioavailability had not been studied in controlled clinical trials. The SPC recommends Firdapse to be taken with food in order to reduce the risk of paraesthesia, dizziness, and upper gastrointestinal pain and nausea; therefore the consequential potential risk of reduced efficacy due to food effect cannot be completely prevented. The Marketing Authorisation Holder undertook a food effect study in healthy volunteers, Study LMS-001.

Data from study LMS-001 were submitted to the EMA as part of the First Annual Reassessment of Firdapse. As a result, SPC Sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) were updated with information for the prescriber regarding the effect of food on Firdapse bioavailability.

Important Identified and Potential Interactions

QTc Prolonging Drugs	
Effect of interaction	See discussion
Evidence source	Theoretical
Possible mechanism	Additive pharmacodynamic effects
Potential health risk	See discussion
Discussion	The potential for an additive effect on QT interval prolongation between Firdapse and QTc prolongation drugs (e.g., sultopride), with a subsequent risk of ventricular arrhythmias, notably TdP, cannot be excluded. This is a theoretical consideration and is not based on controlled clinical data. Precautionary statements are included in the Firdapse SPC (Sections 4.3 and 4.5).

Seizure Threshold Lowering Drugs	
Effect of interaction	See discussion
Evidence source	Theoretical
Possible mechanism	Additive pharmacodynamic effects
Potential health risk	See discussion
Discussion	Seizure threshold lowering drugs (e.g., anti-depressants such as imipraminic compounds, selective serotonin uptake inhibitors, neuroleptics including phenothiazines and butyrophenones, mefloquine, bupropion, and tramadol), in combination with Firdapse may increase risk for seizure. This is a theoretical consideration and is not based on controlled clinical data. Epilepsy is contraindicated in Section 4.3 of the SPC. Precautionary statements regarding seizure and medicinal products known to lower epileptic threshold are included in the Firdapse SPC (Sections 4.4 and 4.5).

Atropinic Drugs	
Effect of interaction	See discussion
Evidence source	Theoretical
Possible mechanism	Increased synaptic ACh concentrations induced by Firdapse may compete with muscarinic ACh antagonists at the ACh receptors
Potential health risk	See discussion
Discussion	In combination with Firdapse, there is a risk of reduced efficacy of atropinic drugs (e.g., tricyclic anti-depressants, most H ₁ atropinic anti-histamines, anticholinergic anti-Parkinson's drugs, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics, and clozapine) though there is no increased risk for undesirable effects. A precautionary statement is included in the SPC (Section 4.5).

Cholinergic Drugs	
Effect of interaction	See discussion
Evidence source	Theoretical
Possible mechanism	Additive or synergistic pharmacodynamic effects
Potential health risk	See discussion
Discussion	Concomitant use of Firdapse with cholinergic drugs (e.g., direct or indirect cholinesterase inhibitors), may result in increased primary and secondary effects of both drugs, due to increased synaptic ACh concentrations from additive or synergistic pharmacodynamic effects. Although this is also a theoretical consideration, not based on controlled clinical data, a precautionary statement is included in the SPC (Section 4.5).

Non-Depolarising Muscle Relaxants	
Effect of interaction	See discussion
Evidence source	Animal and <i>in vitro</i> data
Possible mechanism	Increased synaptic ACh concentrations induced by Firdapse are likely to compete with nicotinic ACh antagonists at the ACh receptors, thereby bearing a potential to decrease the antagonistic effects of non-depolarising muscle relaxants.
Potential health risk	See discussion
Discussion	In combination with Firdapse, there is a potential for reduced efficacy of both the non-depolarising muscle relaxant (e.g., mivacurium and pipercurium) and of Firdapse, though no increased risk for undesirable effects. The clinical relevance of this interaction is unknown; however, a precautionary statement is included in the SPC (Section 4.5).

Depolarising Muscle Relaxants	
Effect of interaction	Theoretical reduced efficacy
Evidence source	Theoretical
Possible mechanism	See discussion
Potential health risk	See discussion
Discussion	In combination with Firdapse, there is a potential for reduced efficacy of both the depolarising muscle relaxant (e.g., suxamethonium) and of Firdapse, though no increased risk for undesirable effects. The clinical relevance of this interaction is unknown; however, a precautionary statement is included in the SPC (Section 4.5).

CYP-Dependently Metabolized Drugs	
Effect of interaction	None identified
Evidence source	See discussion
Possible mechanism	See discussion
Potential health risk	None identified
Discussion	Potent cytochrome (CYP) enzyme inhibitors (e.g., cimetidine, ketoconazole) are not likely to inhibit the metabolism of amifampridine by human N-acetyltransferases (NATs) to give rise to increased amifampridine exposure. The results from an <i>in vitro</i> CYP450 inhibition study indicate that amifampridine does not inhibit the major hepatic CYP450 enzymes. Hence, amifampridine is unlikely to play a role in metabolic-based clinical drug-drug interactions related to inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 metabolism of co-administered drugs. Nonetheless, a precautionary statement is included in the SPC (Section 4.5).

SVII.5: Pharmacological Class Effects

There are no known relevant established class effects beyond the effects of 3,4-DAP already included as important identified or potential risks.

Module SVIII: Summary of the 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 clinical information in paediatric use Lack of information on use during pregnancy and lactation Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants) Lack of photosafety data

PART III: PHARMACOVIGILANCE PLAN

Routine pharmacovigilance activities will be employed for each identified and potential risk in Module SVII. Periodic safety update reports will provide a review of each risk at defined intervals. The LEMS Disease Registry will increase our experience of Firdapse use in LEMS patients. Additional safety data collected through the LEMS Disease Registry for identified and potential risks will also be reported accordingly.

III.1: Safety Concerns and Overview of Planned Pharmacovigilance Actions

Seizures		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Movement Disorders		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Cardiac Toxicity Including QTc Prolongation		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	
Potential for QTc prolongation	Through QTC study (QTC-002)	

Peripheral Vascular Disease/Reynaud's Phenomenon		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Respiratory Disorders Including Bronchospasm		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Hepatotoxicity		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Serious Gastrointestinal Disorders		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Risk of Nerve Sheath Tumour Development (Schwannoma in rats)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Food-Drug Interaction		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LMS-001 Study (completed)	Food interaction study in healthy volunteers
	LMS-002 Study	

Limited Information on Use In Patients With Renal Impairment		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Lack of Information on Use In Patients With Hepatic Disease		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	
	LMS-002 Study	

Lack of Clinical Information In Paediatric Use		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	

Lack of Information on Use During Pregnancy And Lactation		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	

Lack of Information on Potential Drug-Drug Interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, depolarising and non-depolarising muscle relaxants, CYP-dependently metabolised drugs)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	

Lack of Photosafety Data		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	Routine pharmacovigilance	
	LEMS Disease Registry (LEMS-001)	

III.2: Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

None.

III.3: Studies and Other Activities Completed Since Last Update of Pharmacovigilance Plan

Study/Activity Title	
Safety concern(s)/risk minimisation measure investigated	Non-clinical 2-year rat dietary carcinogenicity study (BMN125-13-026)
Brief summary of results	Rats administered BMN 125 had a dose-dependent increase in survival that was associated with decreased food consumption and decreased body weight gain and terminal body weight compared to untreated (control group) rats. Male rats given ≥ 25 mg/kg/day and females given ≥ 8 mg/kg/day had small but statistically significant dose-related increases in the incidence of Schwannomas in both genders. To date, no reports of Schwannoma have been reported in humans treated with amifampridine phosphate. A review of the literature revealed one report of an event of gastric Schwannoma in a patient with LEMS who had received 3,4-DAP. The authors concluded that the event was highly confounded, and their assessment was that the Schwannoma was likely present at the onset of the LEMS diagnosis (Patanella, 2010, Muscle Nerve). Rats of both genders administered amifampridine had increased survival relative to untreated controls. Increased survival in female rats was associated with increased incidence of late-onset (age-related) endometrial carcinomas arising from a non-genotoxic mechanism unrelated to the administration of amifampridine.
Implications	Unknown

III.4: Details of Outstanding Additional Pharmacovigilance Activities

III.4.1: Imposed Mandatory Additional Pharmacovigilance Activity (key to benefit risk)

No category 1 activities have been identified.

III.4.2: Mandatory Additional PhV Activity (being a Specific Obligation)**Category 2: Specific Obligations**

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
1	BMN125-10-038: In Vitro Metabolism of ¹⁴ C-BMN125 by Rat, Rabbit, Dog, Monkey, Mini-pig and Human Hepatocytes	Final study report	31 January 2011
2	BMN125-10-040: Identification of Human Cytochromes P450 and N-Acetyltransferase Enzymes Involved in the Metabolism of ¹⁴ C-BMN125	Final study report	31 January 2011
3	BMN125-10-042: Determination of the Apparent Permeability of ¹⁴ C-BMN125 through Caco-2 Monolayers and Evaluation as a P-gp Substrate and Inhibitor	Final study report	31 January 2011
4	BMN125-10-053: In situ Assessment of the Induction Potential of BMN125 in Primary Cultures of Human Hepatocytes	Final study report	31 January 2011
5	BMN125-10-054: In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of BMN125	Final study report	31 January 2011
6	BMN125-10-004: [¹⁴ C]3,4-Diaminopyridine Phosphate PK and Excretion Studies in the Dog after Single Intravenous and Oral Dosing	Final study report	1 December 2010
7	BMN125-10-005: [¹⁴ C]3,4-Diaminopyridine Phosphate Absorption, Distribution and Excretion Studies in the Rat after Single Oral and IV Dosing	Final study report	1 December 2010
8	BMN125-10-006: [¹⁴ C]3,4-Diaminopyridine Phosphate Metabolite Profiling and Identification Studies in Rats and Dogs after Single Dosing	Final study report	1 December 2010
9	BMN125-10-055: 13-Week Three Times Daily Oral Gavage Toxicity and Toxicokinetic Study with BMN125 in Rats with a 4-Week Recovery Phase.	Final study report	30 June 2011

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
10	QTC-002: A Phase 1, Double-Blind, Randomized, Crossover Study to Define the ECG Effects of Amifampridine Phosphate Using a Therapeutic and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women Who Are Slow Acetylators: A Thorough QT Study.	Final study report	2 January 2014
11	BMN125-13-012: Combination Fertility and Developmental Toxicity Study of BMN 125 Administered to Rats by Oral Gavage	Final study report	19 September 2013
12	BMN125-13-025: Oral Gavage Developmental and Perinatal/Postnatal Reproduction Toxicity Study of BMN 125 in Rats, Including Postnatal Behavioral/Functional Evaluation	Final study report	04 March 2014
13	BMN125-13-014: Dose Range Finding Oral Gavage Developmental and Reproductive Toxicity and Toxicokinetic Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Final study report	30 September 2013
14	BMN125-13-015: Definitive Oral Gavage Developmental and Reproductive Toxicity Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Final study report	17 October 2013
15	BMN125-13-011: 3-Week Palatability and Toxicokinetic Dietary Study for BMN 125 in Rats	Final study report	18 November 2014
16	BMN125-13-026: 104-Week Dietary Carcinogenicity Study with BMN 125 in Rats	Protocol submission	17 June 2013
		Study start	24 June 2013
		Study finish	July 2015
		Final study report	30 June 2016
17	LEMS-01: Lambert-Eaton Myasthenic Syndrome (LEMS) Registry	Protocol submission	14 December 2009
		Study start	5 May 2010
		Study finish	Estimated 2019
		First annual update study report	30 September 2011 (additional annual interim reports each February)
		Final study report	Anticipated 2019

III.4.3: Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or To Measure Effectiveness of Risk Minimisation Measures

Category 3: Required additional pharmacovigilance activities

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
1	LMS-001: Phase 1 food effect study in Healthy Volunteers	Study start	23 June 2010
		Study finish	23 August 2010
		Final study report	14 February 2011
2	FIR-001: A Phase 1, 2-part, Open Label Pharmacokinetic and Safety Study to Evaluate Dose Proportionality and Accumulation of Firdapse (3,4-Diaminopyridine Phosphate) after Single and Multiple Oral Doses in Healthy Volunteers	Final study report	23 February 2012
3	LMS-002: A Phase 3, Multicenter, Double-blind, Placebo-controlled Randomized Discontinuation Study Followed by an Open-label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with LEMS	Protocol submission	8 December 2010
		Study start	6 June 2011
		Study finish	Ongoing
		Interim study report	February 2016
		Final study report	Anticipated September 2017

III.4.4: Stated Additional Pharmacovigilance Activities

None.

III.5: Summary of the Post-Authorisation Pharmacovigilance Development Plan**III.5.1: Table of On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan**

Study/Activity and Objectives	Safety Concerns Addressed	Status	Date for Submission Of Interim Or Final Reports
LEMS-01: Lambert-Eaton Myasthenic Syndrome (LEMS) Registry Primary Objective: To obtain observational safety data (identification, frequency, and severity) on patients diagnosed with LEMS.	All important identified and potential risks, or topics with missing information	Ongoing	Annual interim reports each February Final CSR anticipated February 2019
LMS-002: A Phase 3, Multicenter, Double-blind, Placebo-controlled Randomized Discontinuation Study Followed by an Open-label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with LEMS	All important identified and potential risks, or topics with missing information	Ongoing	Interim report February 2016 Final CSR anticipated September 2017

III.5.2: Table of Completed Studies from the Post-Authorisation Pharmacovigilance Development Plan

Study/Activity And Objectives	Safety Concerns Addressed	Status	Date for Submission Of Final Report
BMN125-10-038: In Vitro Metabolism of ¹⁴ C-BMN125 by Rat, Rabbit, Dog, Monkey, Mini-pig and Human Hepatocytes	Lack of non-clinical data	Completed	31 January 2011
BMN125-10-040: Identification of Human Cytochromes P450 and N-Acetyltransferase Enzymes Involved in the Metabolism of ¹⁴ C-BMN125	Lack of non-clinical data	Completed	31 January 2011
BMN125-10-042: Determination of the Apparent Permeability of ¹⁴ C-BMN125 through Caco-2 Monolayers and Evaluation as a P-gp Substrate and Inhibitor	Lack of non-clinical data	Completed	31 January 2011
BMN125-10-053: In situ Assessment of the Induction Potential of BMN125 in Primary Cultures of Human Hepatocytes	Lack of non-clinical data	Completed	31 January 2011
BMN125-10-054: In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of BMN125	Lack of non-clinical data	Completed	31 January 2011
BMN125-10-004: [¹⁴ C]3,4-Diaminopyridine Phosphate PK and Excretion Studies in the Dog after Single Intravenous and Oral Dosing	Lack of non-clinical data	Completed	1 December 2010
BMN125-10-005: [¹⁴ C]3,4-Diaminopyridine Phosphate Absorption, Distribution and Excretion Studies in the Rat after Single Oral and IV Dosing	Lack of non-clinical data	Completed	1 December 2010
BMN125-10-006: [¹⁴ C]3,4-Diaminopyridine Phosphate Metabolite Profiling and Identification Studies in Rats and Dogs after Single Dosing	Lack of non-clinical data	Completed	1 December 2010
BMN125-10-055: 13-Week Three Times Daily Oral Gavage Toxicity and Toxicokinetic Study with BMN125 in Rats with a 4-Week Recovery Phase.	Lack of non-clinical data	Completed	30 June 2011

Study/Activity And Objectives	Safety Concerns Addressed	Status	Date for Submission Of Final Report
BMN125-13-012: Combination Fertility and Developmental Toxicity Study of BMN 125 Administered to Rats by Oral Gavage	Lack of non-clinical data	Completed	08 November 2013
BMN125-13-025: Oral Gavage Developmental and Perinatal/Postnatal Reproduction Toxicity Study of BMN 125 in Rats, Including Postnatal Behavioral/Functional Evaluation	Lack of non-clinical data	Completed	04 March 2014
BMN125-13-014: Dose Range Finding Oral Gavage Developmental and Reproductive Toxicity and Toxicokinetic Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Lack of non-clinical data	Completed	30 September 2013
BMN125-13-015: Definitive Oral Gavage Developmental and Reproductive Toxicity Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Lack of non-clinical data	Completed	08 November 2013
LMS-001: Phase 1 food effect study in Healthy Volunteers Primary objective: To compare the effect of food on the relative bioavailability of a single dose of amifampridine phosphate, 2 tablets administered orally, during fasting and fed conditions in healthy subjects.	Food-drug interaction	Completed	22 September 2011
FIR-001: A Phase 1, 2-part, Open Label Pharmacokinetic and Safety Study to Evaluate Dose Proportionality and Accumulation of Firdapse (3,4-Diaminopyridine Phosphate) after Single and Multiple Oral Doses in Healthy Volunteers Primary objective: To assess the safety and tolerability of Firdapse after single and multiple doses	Food-drug interaction	Completed	23 February 2012

Study/Activity And Objectives	Safety Concerns Addressed	Status	Date for Submission Of Final Report
QTC-002: A Phase 1, Double-Blind, Randomized, Crossover Study to Define the ECG Effects of Amifampridine Phosphate Using a Therapeutic and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women Who Are Slow Acetylators: A Thorough QT Study. Primary objective: To assess the steady-state effects of a single therapeutic and supra-therapeutic dose of amifampridine phosphate compared with placebo on ECG parameters in healthy adult male and female subjects who are slow acetylators.	Cardiac toxicity including QTc prolongation	Completed	2 January 2014
BMN125-13-011: 3-Week Palatability and Toxicokinetic Dietary Study for BMN 125 in Rats	Lack of non-clinical data	Completed	18 November 2014
BMN125-13-026: 104-Week Dietary Carcinogenicity Study with BMN 125 in Rats	Lack of non-clinical data on carcinogenicity	Completed	30 June 2016

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1: Summary of Existing Efficacy Data (by product and indication)

Firdapse is an orphan drug (EU/3/02/124) designated as such on 18 December 2002. The estimated prevalence of LEMS in the European is approximately 1:100,000.

Management of patients with LEMS can be classified into 3 main categories, each targeting different aspects of the pathogenesis of the disease: 1) anti-tumor treatment (surgery, radiation, chemotherapy) in paraneoplastic LEMS; 2) immunologic treatments (intravenous immunoglobulin, plasma exchange, prednisone, azathioprine, cyclosporine) to suppress anti-VGCC; and 3) symptomatic treatment (pyridostigmine, amifampridine) acting at the NMJ ([Verschuuren, 2006, Expert.Opin.Pharmacother.](#)).

Benefits of Firdapse Treatment for LEMS

Symptomatic treatment is integral to the management of LEMS, and typically is started prior to immunotherapy. Aminopyridines, such as amifampridine, are a mainstay of symptomatic therapy for patients with LEMS ([Skeie, 2006, Eur.J.Neurol.](#)).

Amifampridine is recognized as first line symptomatic treatment for LEMS as reflected in the recommendation of the European Federation of Neurological Societies (EFNS) Task Force. Specifically, amifampridine (3,4-DAP) is a non-specific voltage-dependent potassium (K⁺) channel blocker. The blockade of K⁺ channels causes depolarization of the presynaptic membrane and slows down or inhibits repolarization. Prolonged depolarization results in opening of slow voltage-dependent calcium (Ca²⁺) channels and allows a subsequent influx of Ca²⁺. The increased concentration of intracellular Ca²⁺ induces exocytosis of the synaptic vesicles containing acetylcholine (ACh), thus releasing an increased level of ACh into the synaptic cleft ([Maddison P, 1998, Muscle Nerve](#)), ([Thomsen, 1983, J.Pharmacol.Exp.Ther.](#)). The influx of ACh into the presynaptic cleft enhances neuromuscular transmission, providing improved muscle function.

Clinical Data at Marketing Authorisation

The clinical data for Firdapse prior to Marketing Authorisation originated primarily from published clinical trials using 3,4-DAP rather than a classical clinical development program, and one bioequivalence study (DAPSEL) conducted with tablets containing 3,4-DAP phosphate and capsules containing 3,4-DAP free base.

Clinical efficacy data for the symptomatic treatment of patients with LEMS with amifampridine base are derived from five published randomized, double-blind, placebo controlled studies and one double-blind study with an active comparator (reported in abstract form only) in patients with LEMS. The data from the randomized controlled studies demonstrate statistically significant improvements across a number of independent measures of neurological function, including Quantitative Myasthenia Gravis

(QMG) score and CMAP, which have been demonstrated to be clinically relevant in patients with LEMS.

Results of these trials demonstrate that amifampridine is more effective for the symptomatic treatment of LEMS compared with placebo or active investigational comparator (pyridostigmine). Additionally, supportive data from multiple published uncontrolled investigations and case reports in patients with LEMS demonstrate the long-term benefits of treatment with amifampridine in patients with LEMS. These data also show that removal of patients from drug can lead to a recurrence of underlying symptoms, but with reintroduction of amifampridine improvement of muscle function is regained. As such, amifampridine has been recommended as first-line symptomatic treatment for LEMS by the EFNS ([Skeie, 2006, Eur.J.Neurol.](#)).

Although the results from the published studies ([McEvoy, 1989, N.Engl.J.Med.](#)); ([Sanders, 2000, Neurology](#)); ([Murray, 1984, J Neurol Neurosurg Psychiat](#)), ([Wirtz, 2002, Neuromuscul Disord](#)) and ([Sanders, 1993, Ann.N.Y.Acad.Sci.](#)) were obtained using the base formulation of amifampridine, the results of these studies are applicable to the phosphate formulation because both the phosphate and base forms have been demonstrated to be bioequivalent.

IV.1.1: Applicability to Patients in the Target Population

Clinical efficacy data for the symptomatic treatment of patients with LEMS with amifampridine phosphate base are derived from five published randomized, double-blind, placebo controlled studies and one double-blind study with an active comparator (reported in abstract form only) in patients with LEMS. The data from the randomized controlled studies demonstrate statistically significant improvements across a number of independent measures of neurological function, including Quantitative Myasthenia Gravis (QMG) score and CMAP, which have been demonstrated to be clinically relevant in patients with LEMS.

While future efficacy studies post-authorisation may be conducted, they are not necessary to fill in gaps in knowledge about efficacy in the target population.

IV.2: Tables of Post-Authorisation Efficacy Studies

No post-authorisation efficacy studies that are specific obligations and/or conditions of the MA have been planned or required.

PART V: RISK MINIMISATION MEASURES

Routine risk minimisation measures will include post-marketing aggregate safety reporting (e.g., PSURs), product labeling, regular signal detection, literature review, and RMP planning (including close monitoring of important potential and identified risks to better characterize those risks, updating the RMP as new, relevant information is identified that changes the drug's safety profile, or updating the RMP when specifically requested by a Competent Authority or when there are significant changes to Good Pharmacovigilance Practices or regulatory requirements necessitating such a change).

V.1: Risk Minimisation Measures by Safety Concern

Seizures	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate physicians and patients on potential risk of seizures associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Contraindication for patients with epilepsy Warning/ precaution statement on seizure, including risk minimization recommendations: • Description of risk groups and dose dependency • Recommendations for treatment discontinuation Interactions section includes statement on seizure threshold lowering drugs Listed as an undesirable effect
	Serious reactions appear to be rare in adequately dosed patients without risk factors, and manageable with treatment discontinuation and symptomatic therapy. Assumed risk group is identified. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Movement Disorders	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of movement disorders associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Chorea and myoclonia listed as undesirable effects
	Potential risk based on isolated case reports with unknown causal relationship. No predictive test known. Need for risk minimization measures to be re-assessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Cardiac Toxicity Including QTc Prolongation	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of QT prolongation and related contraindications associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Contraindications: • for patients taking sultopride • in patients with congenital QT syndromes • for patients taking drugs with a known potential to cause QTc prolongation Warning/ precaution statement on clinical and ECG monitoring at initiation of the treatment, yearly thereafter, and immediately in case of signs and symptoms indicative of cardiac arrhythmias Cardiac rhythm disorders listed as undesirable effect Precautionary action based on isolated reports and possible pharmacological effects; to date no evidence for serious reactions such as TdP or ventricular tachycardia. Assumed risk groups clearly identified. No predictive test known. Need for risk minimization measures to be re-assessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Peripheral Vascular Disorders/Raynaud's Phenomenon	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of Peripheral Vascular disease/ Raynauds phenomenon associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Listed as an undesirable effect
	Precautionary action based on isolated reports and possible pharmacological effects; to date no evidence for serious reactions. No predictive test known. Need for risk minimization measures to be re-assessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Respiratory Disorders Including Bronchospasm	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of bronchospasm associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Contraindication for patients with uncontrolled asthma Warning/ precaution that asthma patients should be closely monitored Cough, bronchial hypersecretion, asthma attack in asthmatic patients or patients with a history of asthma are listed as undesirable effect
	Precautionary action based on isolated reports and possible pharmacological effects; to date no evidence for serious reactions. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Hepatotoxicity	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of hepatotoxicity associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Warnings and Precautions for careful monitoring and slower dose titration in patients with hepatic impairment Elevated liver function tests listed as undesirable effect
	Precautionary action based on isolated reports. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness Of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Serious Gastrointestinal Conditions	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of serious gastrointestinal conditions associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Epigastralgia, diarrhoea, nausea, and abdominal pain listed as undesirable effects No labelling regarding serious gastrointestinal conditions
	Precautionary action based possible pharmacological effects and observed non-serious reactions; to date no evidence for serious reactions. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Risk of Nerve Sheath Tumour Development (Schwannoma in rats)	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential risk of possible nerve sheath tumour development (and Schwannoma in particular) associated with use of amifampridine phosphate
Routine risk minimisation measures	<u>Labelling:</u> Warnings and Precautions (Section 4.4) for use in patients with an increased risk for nerve sheath tumours. Section 5.3 of the SPC provides information on nerve sheath tumour development in rats treated with Firdapse.
	Precautionary action based on possible pharmacological effects and observed non-clinical data; to date no evidence for nerve sheath tumour development. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Food-Drug Interaction	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients on potential of effect of food on bioavailability of Firdapse.
Routine risk minimisation measures	<u>Labelling:</u> Sections 4.2 and 5.2 of the SPC provide information on effect of food on bioavailability of Firdapse.
	Precautionary action based on possible pharmacological effects and healthy volunteer PK data from study LMS-001; to date there are lack of data on correlation between reduced plasma concentration and lack of efficacy. No predictive test known. Need for risk minimization measures to be re-assessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Limited Information on use in Patients with Renal Impairment	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients who fall into certain important subgroups that there is limited information surrounding the use of amifampridine phosphate in these subgroups
Routine risk minimisation measures	<u>Labelling:</u> Warnings/ precautions section: Recommends slow titration of dose and close monitoring of patients with renal impairment, and advises to discontinue upward dose titration if adverse reactions occur. Pharmacokinetic properties section discusses PK findings in patients with renal impairment
	Based on the assumed metabolism and elimination pathways, caution in patients with renal impairment is considered an appropriate precautionary risk minimization measure. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Lack of Information on use in Patients with Hepatic Disease	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients who fall into certain important subgroups that there is missing information surrounding the use of amifampridine phosphate in these subgroups
Routine risk minimisation measures	<u>Labelling:</u> Warnings/ precautions section: Communicates lack of information regarding patients with hepatic disease; Recommends close monitoring of patients with hepatic impairment; and Advises that dose adjustment may be needed in this patient group.
	Based on the assumed metabolism and elimination pathways, caution in patients with hepatic disease is considered an appropriate precautionary risk minimization measure. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Lack of Clinical Information in Paediatric Use	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients that there is missing information surrounding the use of amifampridine phosphate in pediatric population due to limited experience
Routine risk minimisation measures	<u>Labelling:</u> SPC states that use in this patient group is not recommended due to lack of data on safety and efficacy.
	No specific safety concern in this population. Communication of lack of information is considered appropriate. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Lack of Information on use During Pregnancy and Lactation	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients missing information surrounding the use of amifampridine phosphate during pregnancy, and breast feeding due to limited information available.
Routine risk minimisation measures	<u>Labelling:</u> Fertility, pregnancy/lactation section states that Firdapse should not be used during pregnancy, and that women of childbearing potential must use effective contraception during Firdapse treatment. Use during breastfeeding should be decided based on the benefit of breastfeeding for the child and the benefit of continued Firdapse therapy for the mother.
	Limited data, but no indication towards clinically relevant reproductive toxicity. Communication of limited information is considered appropriate. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Lack of Information on Potential Drug-Drug Interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants)	
Objectives of the risk minimisation measures	The objective of the risk minimisation measures detailed below is to educate patients of potential drug-drug interactions on patients taking drugs that could prolong QTc interval, as there is missing information surrounding the use of amifampridine phosphate in these subgroups
Routine risk minimisation measures	<u>Labelling:</u> Contraindication section communicates potential interactions with drugs with TdP and/or QTc prolonging potential Warning/precaution regarding use of amifampridine concomitantly with seizure-threshold lowering drugs
	Communication of lack of information is considered appropriate. No predictive test known. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

Lack of Photosafety Data	
Objectives of the risk minimisation measures	Objective of this measure is to educate patients on lack of long term effects due to limited photosafety data available.
Routine risk minimisation measures	<u>Labelling:</u> Currently none
	Identified as missing information due to absence of non-clinical data. No indication from bibliographical or clinical data of a risk. Need for risk minimization measures to be reassessed if pharmacovigilance activities reveal a specific concern.
Effectiveness of Risk Minimisation Measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of labeling will be measured by monitoring therapeutic effectiveness data, the rate and nature of reported and/or solicited adverse events, and prescribing patterns to verify proper usage in the post-marketing setting. Collected data will be evaluated to detect possible differences between pre- and post-marketing populations, and whether these differences impact the risk-benefit balance of Firdapse.
Criteria for judging the success of the proposed risk minimisation measures	Criteria for judging the success of the proposed risk minimisation intervention (i.e., labeling) will be: • Consistency of pre- and post-marketing efficacy and effectiveness data with longer-term exposure; • Consistency of safety profile with longer-term exposure; and • Verification of proper use of Firdapse based on registry usage data.
Planned dates for assessment	Assessment of aggregate safety data will be performed on an ongoing basis and findings summarized in periodic risk-benefit evaluation reports at required time intervals. In addition, results from ongoing studies will be provided in clinical study reports once the studies are complete.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable

V.2: Risk Minimisation Measure Failure

Not applicable.

V.2.1: Analysis of Risk Minimisation Measure(s) Failure

Not applicable.

V.2.2: Revised Proposal for Risk Minimisation

Not applicable.

V.3: Summary Table of Risk Minimisation Measures

Safety Concern	Additional Risk Minimisation Measures	Routine Risk Minimisation Measures
Seizures	None identified	Product Information
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)		
Food-drug interaction		
Limited information on use in patients with renal impairment		
Lack of information on use in patients with hepatic disease		
Lack of clinical information in paediatric use		
Lack of information on use during pregnancy and lactation		
Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants)		
Lack of photosafety data		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT**VI.1 Elements for Summary Tables in the EPAR****VI.1.1 Summary Table of 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 clinical information in paediatric use Lack of information on use during pregnancy and lactation Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants) Lack of photosafety data

**VI.1.2 Table of on-Going and Planned Studies in the Post-Authorisation
Pharmacovigilance Development Plan**

Study/Activity and Objectives	Safety Concerns Addressed	Status	Date For Submission Of Interim Or Final Reports
LEMS-01: Lambert-Eaton Myasthenic Syndrome (LEMS) Registry Primary Objective: To obtain observational safety data (identification, frequency, and severity) on patients diagnosed with LEMS.	All important identified and potential risks, or topics with missing information	Ongoing	Annual interim reports each February Final CSR anticipated February 2019
LMS-002: A Phase 3, Multicenter, Double-blind, Placebo-controlled Randomized Discontinuation Study Followed by an Open-label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with LEMS	All important identified and potential risks, or topics with missing information	Ongoing	Interim report February 2016 Final CSR anticipated September 2017

VI.1.3 Summary of Post-Authorisation Efficacy Development Plan

No post-authorisation efficacy studies that are specific obligations and/or conditions of the MA have been planned or required.

VI.1.4 Summary Table of Risk Minimisation Measures

Safety Concern	Additional Risk Minimisation Measures	Routine Risk Minimisation Measures
Seizures	None identified	Product Information
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)		
Food-drug interaction		
Limited information on use in patients with renal impairment		
Lack of information on use in patients with hepatic disease		
Lack of clinical information in paediatric use		
Lack of information on use during pregnancy and lactation		
Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants)		
Lack of photosafety data		

VI.2 Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder in which patients have muscle weakness because of a failure of the nerves to transmit electrical impulses to the muscles. Because the number of patients with LEMS is low, the disease is considered 'rare', and Firdapse was designated an 'orphan medicine' (a medicine used in rare diseases) on 18 December 2002.

VI.2.2. Summary of Treatment Benefits

What is Firdapse Used For?

Firdapse is a pill used to treat LEMS symptoms in adults.

How is Firdapse Used?

The dose of Firdapse is established by the treating doctor based on the intensity of the symptoms and certain genetic factors of the patient.

How does Firdapse Work?

In patients suffering from this disease, a chemical substance called acetylcholine, which communicates nerve impulses to muscles, is not released normally and the muscle doesn't receive some or all of the nerve's signals. Firdapse works by increasing the release of acetylcholine and helps the muscle to receive the nerve signals.

How Has Firdapse Been Studied?

In two published studies involving a total of 38 adults with LEMS, Firdapse was compared with placebo (a dummy treatment). The main measures of effectiveness were based on the rating of how well the muscles worked using scoring systems for nerve function and muscle strength. Another study combined data from the two published studies and looked at the intensity of muscle activity.

What Benefit has Firdapse Shown During the Studies?

Adults treated with Firdapse showed improvements in nerve function and muscle strength.

VI.2.3 Unknowns Relating to Treatment Benefits

The group of clinical studies/ literature articles that have been used to study Firdapse have included patients of different ages, genders, and racial/ethnic and geographical backgrounds. A review of the results of these studies has not shown any difference in safety or effectiveness of based on any of those characteristics. There are still groups of patients which have not been closely studied (such as women who are pregnant or breastfeeding, or patients with liver problems). It is not known whether Firdapse will have a different effect or will be less safe to use in these groups.

VI.2.4. Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Seizures	Exposure to Firdapse is associated with an increased risk for epileptic seizures.	Patients who have a history of seizures should not take Firdapse. In patients who are at risk for a seizure, Firdapse will be used conservatively.
Food drug interaction	Taking Firdapse on an empty stomach may lead to stomach pain or other problems.	Patients should take Firdapse with food to help prevent the stomach aches and other stomach problems.

Important Potential Risks

Risk	What is Known
Movement disorders	Firdapse may cause uncontrolled bodily movements or muscle spasms and twitching
Irregular heartbeat or other bad effects on the heart (Cardiac toxicity including QTc prolongation)	Firdapse may cause your heart to beat irregularly, or faster than normal
Decreased blood flow to the hands and feet, particularly in response to cold (Peripheral vascular disorders/Raynaud's phenomenon)	Firdapse may cause problems with getting blood circulating to your hands and feet, making them feel cold or tingly. This may be particularly true in cold weather, or when you put your hands or feet into very cold water.
Lung problems, including sudden narrowing of the airways (Respiratory disorders including bronchospasm)	Firdapse may cause cough and a build-up of mucus in your throat, or it may trigger asthma attacks in patients who have a previous history of asthma.
Liver problems (Hepatotoxicity)	Firdapse may cause increase in certain blood tests that measure whether your liver has been damaged.
Serious gastrointestinal conditions	Firdapse may cause stomach aches, diarrhoea, or nausea (a feeling of being sick to your stomach).
Risk of development of a particular kind of nervous system tumour (Nerve sheath tumour development [Schwannoma in rats])	Firdapse may cause tumours called Schwannomas, that come from the tissue that covers your nerve cells. These tumours can occur anywhere in the body, but are most common in nerves in the arm, leg, or lower back. Even if you have one of these tumours, you may have no symptoms, or you may have back pain or pain, numbness, weakness, or the feeling of a mass under your skin at the area of the tumour. These tumours are usually benign (not malignant or likely to cause serious problems) and can be removed surgically.

Missing Information

Risk	What is Known
Limited information in patients with kidney problems (Limited information on use in patients with renal impairment)	There is limited information available on the use of Firdapse by patients with kidney problems. Patients with kidney problems may need to start treatment with Firdapse at a lower dose and increase the dose more slowly.
Lack of information in patients with liver problems (Lack of information on use in patients with hepatic disease)	Firdapse has not been studied in patients with pre-existing heart or liver disease.
Lack of information in children (Lack of clinical information in paediatric use)	Firdapse has not been studied by giving it to children.
Lack of information in women who are pregnant or breastfeeding (Lack of information on use during pregnancy and lactation)	Firdapse has not been studied in pregnant or breastfeeding women. It is recommended that women using Firdapse not get pregnant, and they are advised that they must use effective contraception
Lack of information on potential drug-drug interactions (Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants))	Some drugs, when taken together, may interact with each other to cause new problems that would not normally occur when a drug is taken by itself. The possible side effects of taking Firdapse with other drugs (including other drugs which might cause a particular type of irregular heartbeat, or other drugs which might make you more prone to having a seizure) have not been studied.
Lack of information on sun exposure in Firdapse patients (Lack of photosafety data)	There is limited information available on whether taking Firdapse might make your skin more sensitive to sunlight, or cause other bad side effects related to exposure to sunlight.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks of the medicine, and recommendations for minimising those risks. An abbreviated version of this SPC, in lay language, is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The SPC and the PL for Firdapse can be found in Annex 2.

This medicine has no additional risk minimisation measures.

VI.2.6. Planned Post-Authorisation Development Plan**List of Studies in Post-Authorisation Development Plan**

Study/Activity and Objectives	Safety Concerns Addressed	Status	Date For Submission Of Interim Or Final Reports
BMN125-13-012: Combination Fertility and Developmental Toxicity Study of BMN 125 Administered to Rats by Oral Gavage	Lack of non-clinical data	Completed	08 November 2013
BMN125-13-025: Oral Gavage Developmental and Perinatal/Postnatal Reproduction Toxicity Study of BMN 125 in Rats, Including Postnatal Behavioral/Functional Evaluation	Lack of non-clinical data	Completed	04 March 2014
BMN125-13-014: Dose Range Finding Oral Gavage Developmental and Reproductive Toxicity and Toxicokinetic Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Lack of non-clinical data	Completed	30 September 2013
BMN125-13-015: Definitive Oral Gavage Developmental and Reproductive Toxicity Study in Rabbits: BMN 125 Effects on Embryo-Fetal Development	Lack of non-clinical data	Completed	08 November 2013
BMN125-13-011: 3-Week Palatability and Toxicokinetic Dietary Study for BMN 125 in Rats	Lack of non-clinical data	Completed	18 November 2014
BMN125-13-026: 104-Week Dietary Carcinogenicity Study with BMN 125 in Rats	Lack of non-clinical data	Completed	30 June 2016
LEMS-01: Lambert-Eaton Myasthenic Syndrome (LEMS) Registry Primary Objective: To obtain observational safety data (identification, frequency, and severity) on patients diagnosed with LEMS.	All important identified and potential risks, or topics with missing information	Ongoing	Annual interim reports each February Final CSR anticipated February 2019

Study/Activity and Objectives	Safety Concerns Addressed	Status	Date For Submission Of Interim Or Final Reports
QTC-002: A Phase 1, Double-Blind, Randomized, Crossover Study to Define the ECG Effects of Amifampridine Phosphate Using a Therapeutic and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women Who Are Slow Acetylators: A Thorough QT Study. Primary objective: To assess the steady-state effects of a single therapeutic and supra-therapeutic dose of amifampridine phosphate compared with placebo on ECG parameters in healthy adult male and female subjects who are slow acetylators.	Cardiac toxicity including QTc prolongation	Completed	2 January 2014
LMS-002: A Phase 3, Multicenter, Double-blind, Placebo-controlled Randomized Discontinuation Study Followed by an Open-label Extension Period to Evaluate the Efficacy and Safety of Amifampridine Phosphate (3,4-Diaminopyridine Phosphate) in Patients with LEMS	All important identified and potential risks, or topics with missing information	Ongoing	Interim report February 2016 Final CSR anticipated September 2017

Studies Which Are a Condition of the Marketing Authorisation

Study QTC-002, as well as the reproductive toxicity and carcinogenicity non-clinical studies, were Specific Obligations of the Marketing Application. In addition, the LEMS-01 Registry was a Specific Obligation of the Marketing Application.

VI.2.7. Summary of Changes to the Risk Management Plan over Time**Major Changes to the Risk Management Plan over Time**

Version	Date	Safety Concerns	Comment
1.0	23 August 2011	<u>Identified Risks:</u> Seizures <u>Identified interactions with other medicinal products, food, and other substances</u> Food-drug interaction <u>Potential Risks:</u> Movement disorders Cardiac toxicity including QTc prolongation Peripheral vascular disorders/Raynaud's phenomenon Respiratory disorders including bronchospasm Hepatotoxicity Serious gastrointestinal conditions <u>Missing Information:</u> Lack of non-clinical data on reproductive toxicity, carcinogenicity, PK, and long-term toxicity Lack of information on use in patients with hepatic disease or renal impairment Lack of clinical information in paediatric use Lack of information on use during pregnancy and lactation Lack of information on potential drug-drug interactions (including QTc prolonging drugs, seizure threshold reducing drugs, atropinic and cholinergic drugs, and depolarizing and non-depolarizing muscle relaxants) Lack of photosafety data	
2.0	23 February 2012	Food-drug interaction moved from "Important Missing Information" to "Identified Interactions with Other Medicinal Products, Food, and Other Substances"	
3.0	23 August 2012	No change from version 2.0.	
4.0	16 January 2014	No change from version 3.0.	New RMP template
5.0	23 March 2014	No new safety concerns Under Missing information: "Lack of" changed to "Limited", non-clinical data on reproductive toxicity, carcinogenicity, PK, and long-term toxicity non clinical data	
6.0	11 July 2014	No new safety concerns Risks previously identified as "Important Missing Information" are now referred to as "Missing Information"	Revised public summary for consistent lay language

Version	Date	Safety Concerns	Comment
7.0	25 September 2015	Under Missing information: “Lack of” changed to “Limited” for use in patients with renal impairment Removed Under Missing information: Data from non-clinical studies on reproductive toxicity, PK, and long-term toxicity	Added results of study REN-002 and updated exposure
8.0	26 January 2016	Moved “Food-Drug Interaction” to Important Identified Risk	Added reference to completed interim CSR for LMS-002
9.0	22 June 2016	Removed under Missing Information: Limited non-clinical data on carcinogenicity	Added results of non-clinical carcinogenicity study
10.0	4 October 2016	Added “Risk of nerve sheath tumour development (Schwannoma in rats)” as an Important Potential Risk	Changes in response to Type II variation assessment report
11.0	16 February 2017	No change	New SPC added to Annex 2

REFERENCES

The following references are all available upon request from BioMarin.

Bayrak, AO, Sandikci, U, Yon, SK, Onar, MK. Manifestation of Lambert-Eaton myasthenic syndrome during last trimester of pregnancy. *Int J Neurosci* 120[6], 439-441. 2010.

Booker, PD, Whyte, SD, Ladusans, EJ. Long QT syndrome and anaesthesia. *Br J Anaesth* 90[3], 349-366. 2003.

Centre Hospitalier Regional de Rennes. Report on the Safety of Use of 3,4-Diaminopyridine, External report, dated May 2. 2006.

Cull, CA, Fowler, M, Brown, SW. Perceived self-control of seizures in young people with epilepsy. *Seizure* 5[2], 131-138. 1996.

Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J Supplement K*, K70-K80, 2001.

Eagan, TM, Brogger, JC, Eide, GE, Bakke, PS. The incidence of adult asthma: a review. *Int J Tuberc Lung Dis* 9[6], 603-612. 2005.

Eymard, Andriantafika, Raymonenq, Berleur. Retrospective follow-up study of patients with Lambert-Eaton myasthenic syndrome and treated with 3,4-diaminopyridine. *Clinical Study Report, AGEPS* . 2006.

Frucht, MM, Quigg, M, Schwaner, C, Fountain, NB. Distribution of seizure precipitants among epilepsy syndromes. *Epilepsia* 41[12], 1534-1539. 2000.

Hauser, WA, Annegers, JF, Kurland, LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 34[3], 453-468. 1993.

Hedlund, U, Eriksson, K, Ronmark, E. Socio-economic status is related to incidence of asthma and respiratory symptoms in adults. *Eur Respir J* 28[2], 303-310. 2006.

Hernandez-Diaz, S, Rodriguez, LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 55[2], 157-163. 2002.

Ioannou, GN, Boyko, EJ, Lee, SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. *Am J Gastroenterol* 101[1], 76-82. 2006.

Kobau, R, Gilliam, F, Thurman, DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 HealthStyles Survey. *Epilepsia* 47[11], 1915-1921. 2006.

Lecky BRF. Transient neonatal Lambert-Eaton syndrome. *J Neurol Neurosurg Psychiatry* 77, 1094-1102. 2006.

Maddison P, Newsom-Davis J, Mills K. Effect of 3,4 DAP on the time course of decay compound muscle action potential augmentation in the Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 21, 1196-1198. 1998.

Maricq, HR, Carpentier, PH, Weinrich, MC, Keil, JE et. al. Geographic variation in the prevalence of Raynaud's phenomenon: Charleston, SC, USA, vs Tarentaise, Savoie, France. *J Rheumatol* 20[1], 70-76. 1993.

McEvoy, KM, Windebank, AJ, Daube, JR, Low, PA. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 321[23], 1567-1571. 1989.

Murray, Newsome-Davis, Karni., Wiles. Oral 3,4-Diaminopyridine in the Treatment of the Lambert-Eaton Myasthenic Syndrome (LEMS). *J Neurol Neurosurg Psychiatr* 47, 1052-1056. 1984.

Nakken, KO, Solaas, MH, Kjeldsen, MJ, Friis, ML et. al. Which seizure-precipitating factors do patients with epilepsy most frequently report? *Epilepsy Behav* 6[1], 85-89. 2005.

Newsom-Davis, J. Lambert-Eaton myasthenic syndrome. *Rev Neurol (Paris)* 160[2], 177-180. 2004.

Palace, J, Wiles, CM, Newsom-Davis, J. 3,4-Diaminopyridine in the treatment of congenital (hereditary) myasthenia. *J Neurol Neurosurg Psychiatry* 54[12], 1069-1072. 1991.

Patanella, AK, Bianco, A, Federico, F, Modoni, A et al. Lambert-Eaton myasthenic syndrome associated with gastric Schwannoma. *Muscle Nerve* 41, 569-579. 2010.

Peluso-Pellicer, A, Monte-Boquet, E, Roma-Sanchez, E, Casanova-Sorni, C et. al. Fetal exposure to 3,4-diaminopyridine in a pregnant woman with congenital myasthenia syndrome. *Ann Pharmacother* 40[4], 762-766. 2006.

Reuner, U, Kamin, G, Ramantani, G, Reichmann, H et. al. Transient neonatal Lambert-Eaton syndrome. *J Neurol* 255[11], 1827-1828. 2008.

Ries, L, Melbert D, Krapcho M, Mariotto A et. al. Table XV-4. Small cell lung and bronchus cancer (invasive). Age adjusted SEER incidence rates by year, race and sex. SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD. SEER website [based on November 2006 SEER data submission, posted to the SEER web site, 2007 (Accessed 01Mar2008)]. 2007.

Rudd, RA, Moorman, JE. Asthma incidence: data from the National Health Interview Survey, 1980-1996. *J Asthma* 44[1], 65-70. 2007.

Sanders, DB, Howard, JF, Jr., Massey, JM. 3,4-Diaminopyridine in Lambert-Eaton myasthenic syndrome and myasthenia gravis. *Ann N Y Acad Sci* 681, 588-590. 1993.

Sanders, DB. Lambert-Eaton myasthenic syndrome: clinical diagnosis, immune-mediated mechanisms, and update on therapies. *Ann Neurol* 37 Suppl 1, S63-S73. 1995.

Sanders, DB. 3,4-Diaminopyridine (DAP) in the treatment of Lambert-Eaton myasthenic syndrome (LEMS). *Ann N Y Acad Sci* 841, 811-816. 1998.

Sanders, DB, Massey, JM, Sanders, LL, Edwards, LJ. A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome. *Neurology* 54[3], 603-607. 2000.

Sanders, DB. Lambert-eaton myasthenic syndrome: diagnosis and treatment. *Ann N Y Acad Sci* 998, 500-508. 2003.

Schneider-Gold, C, Wessig, C, Hopker, M, Erdlenbruch, B et. al. Pregnancy and delivery of a healthy baby in autoimmune Lambert-Eaton myasthenic syndrome. *J Neurol* 253[9], 1236-1237. 2006.

Skeie, GO, Apostolski, S, Evoli, A, Gilhus, NE et. al. Guidelines for the treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 13[7], 691-699. 2006.

Spatt, J, Langbauer, G, Mamoli, B. Subjective perception of seizure precipitants: results of a questionnaire study. *Seizure* 7[5], 391-395. 1998.

Suter, LG, Murabito, JM, Felson, DT, Fraenkel, L. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum* 52[4], 1259-1263. 2005.

Thomsen, RH, Wilson, DF. Effects of 4-aminopyridine and 3,4-diaminopyridine on transmitter release at the neuromuscular junction. *J Pharmacol Exp Ther* 227[1], 260-265. 1983.

Tim, RW, Massey, JM, Sanders, DB. Lambert-Eaton myasthenic syndrome: electrodiagnostic findings and response to treatment. *Neurology* 54[11], 2176-2178. 2000.

Vandentorren, S, Baldi, I, Annesi, M, I, Charpin, D et. al. Long-term mortality among adults with or without asthma in the PAARC study. *Eur Respir J* 21[3], 462-467. 2003.

Verschuuren, JJ, Wirtz, PW, Titulaer, MJ, Willems, LN et. al. Available treatment options for the management of Lambert-Eaton myasthenic syndrome. *Expert Opin Pharmacother* 7[10], 1323-1336. 2006.

Vinke, M, Lehnen, H. Two uncomplicated pregnancies and births in a patient with long-standing Lambert-Eaton Myasthenic Syndrome. *Geburtschilfe Frauenheilkd* , 367-369. 2007.

Wara, P. Incidence, diagnosis, and natural course of upper gastrointestinal hemorrhage. Prognostic value of clinical factors and endoscopy. *Scand J Gastroenterol Suppl* 137, 26-27. 1987.

Wehrens, XH, Vos, MA, Doevendans, PA, Wellens, HJ. Novel insights in the congenital long QT syndrome. *Ann Intern Med* 137[12], 981-992. 2002.

Wirtz, PW, Nijhuis, MG, Sotodeh, M, Willems, LN et. al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. *J Neurol* 250[6], 698-701. 2003.

Wirtz, P, van Gerven JMA, van Dijk JG1. The effects of 3,4-DAP (DAP) and pyridostigmine (PS) on muscle function in the Lambert-Eaton myasthenic syndrome (LEMS): a double-blind placebo-controlled cross-over study. *Neuromuscul Disord* , 12-760. 2002

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ANNEX 7: Specific Adverse Event Follow-Up Forms

None.

ANNEX 10: Details of Proposed Additional Risk Minimisation Activities

No additional risk minimisation activities have been proposed.