ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

FIRDAPSE 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amifampridine phosphate equivalent to 10 mg of amifampridine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, round tablet, flat-faced on one side and scored on the other side.
The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Posology

FIRDAPSE should be given in divided doses, three or four times a day. The recommended starting dose is 15 mg amifampridine a day, which can be increased in 5 mg increments every 4 to 5 days, to a maximum of 60 mg per day. No single dose should exceed 20 mg.

Tablets are to be taken with food. Please see section 5.2 for further information about bioavailability of amifampridine in the fed and fasted state.

Genetic differences in N-acetyl transferase enzymes can account for the variable systemic exposure of amifampridine (see sections 4.4 and 5.2).

If treatment is discontinued, patients may experience some of the symptoms of LEMS.

Renal or hepatic impairment
FIRDAPSE should be used with caution in patients with renal or hepatic impairment. A starting dose of 5 mg amifampridine (half tablet) once per day is recommended in patients with moderate or severe impairment of renal or hepatic function. For patients with mild impairment of renal or hepatic function, a starting dose of 10 mg amifampridine (5 mg twice a day) per day is recommended. Patients should be titrated more slowly than those without renal or hepatic impairment with doses increased in 5 mg increments every 7 days. If any adverse reaction occurs, upward dose titration should be discontinued (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of FIRDAPSE in children aged 0 to 17 years has not been established. No data are available.

Method of administration

For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1
- Epilepsy
- Uncontrolled asthma
- Concomitant use with sultopride (see sections 4.5 and 5.1)
- Concomitant use with medicinal products with a narrow therapeutic window (see section 4.5)
- Concomitant use with medicinal products with a known potential to cause QTc prolongation
- In patients with congenital QT syndromes (see section 4.4)

4.4 Special warnings and precautions for use

Renal and hepatic impairment

The pharmacokinetics of amifampridine has been assessed in a single dose Phase I study in patients with renal impairment (see section 5.2).

No studies have been conducted in patients with hepatic impairment. In view of the risk of markedly increased exposure to medicinal product, patients with renal or hepatic impairment must be carefully monitored. The dose of amifampridine should be titrated more slowly in patients with renal and hepatic impairment than those with normal renal and hepatic function. Upward dose titration should be discontinued if any adverse reaction occurs (see section 4.2).

Seizures

Exposure to amifampridine is associated with an increased risk for epileptic seizures. The risk of seizures is dose-dependent and is increased in patients with risk factors which lower the epileptic threshold; including use in combination with other medicinal products known to lower the epileptic threshold (see section 4.5). In the event of a seizure, treatment should be discontinued.

Carcinogenicity risk

In a 2-year dietary carcinogenicity study, benign and malignant Schwannomas have been observed in rats treated with amifampridine (see section 5.3). Amifampridine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests. The correlation between the use of amifampridine and the development of tumours in humans is unknown at this time.

Most Schwannomas are benign and asymptomatic. They can present in many locations, therefore the clinical presentation can be varied. A diagnosis of Schwannoma should be considered for patients who present with symptoms such as a mass that is painful on palpation or symptoms similar to a compressive neuropathy. Schwannomas are generally slow-growing and can exist for months to years without producing symptoms. The benefit of continuing treatment with amifampridine should be reviewed for any patient who develops a Schwannoma.

Amifampridine should be used with caution in patients with an increased risk of Schwannomas, such as patients with past medical history of such tumours, neurofibromatosis Type 2 or schwannomatosis.

Cardiac effects

Clinical and electrocardiogram (ECG) monitoring are indicated at the initiation of the treatment and yearly thereafter. In case of signs and symptoms indicative of cardiac arrhythmias, ECG should be performed immediately. No clinically relevant ECG morphological changes following administration of amifampridine phosphate were observed in a study of healthy volunteers (see section 5.1).

Concomitant diseases

Patients must be told to inform any physician they consult that they are taking this medicinal product, since close monitoring of a concomitant disease, particularly asthma, may be necessary.

Acetylation status

The pharmacokinetics and systemic exposure to amifampridine is notably influenced by the overall metabolic acetylation activity of the polymorphic N-acetyl-transferase (NAT) enzymes (acetylator phenotype) and NAT2 genotype, which is subject to genetic variation (see section 5.2), as shown in the healthy volunteer study. In this study, slow acetylators experienced more adverse reactions than the fast acetylators. The safety profile in this study is consistent with adverse reactions observed with patients on FIRDAPSE.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Medicinal products eliminated through metabolism or active secretion
There are no data on the effects of amifampridine on the metabolism or active secretion of other medicinal products. Thus, special care should be taken in patients undergoing concomitant treatment with medicinal products eliminated through metabolism or active secretion. Monitoring is advised when possible. The dose of the concomitantly given medicinal product should be adjusted if necessary. Concomitant use of medicinal products with a narrow therapeutic window is contraindicated (see section 4.3).

Substances which are potent inhibitors of enzymes that metabolise medicinal products (see section 5.2)
Potent cytochrome P450 (CYP450) enzyme inhibitors e.g. cimetidine, ketoconazole are not likely to inhibit the metabolism of amifampridine by human NATs giving rise to increased amifampridine exposure. The results from the *in vitro* CYP450 inhibition study indicate 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 medicinal products. Regardless, patients should be closely monitored for adverse reactions when initiating treatment with a potent enzyme or renal transporter inhibitor. If treatment with a potent inhibitor is discontinued, patients should be monitored for efficacy as an increase of amifampridine dose may be necessary.

Substances which are potent inducers of enzymes that metabolise medicinal products (see section 5.2)
The results from *in vitro* studies suggest there is low potential for drug-drug interactions due to enzyme induction of CYP1A2, CYP2B6, and CYP3A4 enzymes by amifampridine.

Pharmacodynamic interactions

Based on the pharmacodynamic properties of amifampridine, the concomitant use with sultopride or other medicinal products known to cause QT prolongation (e.g., disopyramide, cisapride, domperidone, rifampicin and ketoconazole) is contraindicated as this combination may lead to an enhanced risk of ventricular tachycardia, notably torsade de pointes (see sections 4.3 and 5.1).

Combinations requiring precautions for use

Medicinal products known to lower the epileptic threshold
The concomitant use of amifampridine and substances known to lower the epileptic threshold may lead to an increased risk of seizures. The decision to administer proconvulsant or epileptic-threshold lowering substances concomitantly should be carefully considered in the light of the severity of the associated risks. These substances include most anti-depressants (tricyclic antidepressants, selective serotonin uptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, bupropion and tramadol (see sections 4.4 and 5.1).

Combinations to be taken into consideration

Medicinal products with atropinic effects
The concomitant use of FIRDAPSE and medicinal products with atropinic effects may reduce the effect of both active substances and should be taken into consideration. Medicinal products with atropinic effects include tricyclic anti-depressants, most H1 atropinic anti-histamines, anticholinergic, anti-Parkinson medicinal products, atropinic antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine.

Medicinal products with cholinergic effects
The concomitant use of FIRDAPSE and medicinal products with cholinergic effects (e.g. direct or indirect cholinesterase inhibitors) may lead to an increased effect of both products and should be taken into consideration.

Non depolarising muscle relaxant acting medicinal products
The concomitant use of FIRDAPSE and medicinal products with non-depolarising muscle relaxant effects (e.g. mivacurium, pipercurium) may lead to a decreased effect of both products and should be taken into consideration.

Depolarising muscle relaxant acting medicinal products
The concomitant use of FIRDAPSE and medicinal products with depolarising muscle relaxant effects (e.g. suxamethonium) may lead to a decreased effect of both products and should be taken into consideration.

4.6 Fertility, pregnancy and lactation

Pregnancy

FIRDAPSE should not be used during pregnancy. Women of childbearing potential must use effective contraception during FIRDAPSE treatment. No adequate clinical data on exposed pregnancies are available for amifampridine. Amifampridine has shown no effect on embryo-foetal viability and development in rabbits; however, in rats, an increase in the number of mothers delivering still-born offspring was observed (see section 5.3).

Breast-feeding

It is unknown whether amifampridine is excreted in human breast milk. Available reproductive data in animals have shown presence of amifampridine in milk of breast-feeding mothers. Assessment of breast-feeding neo-natal animals showed no indication of adverse reactions when exposed to amifampridine through breast-milk. 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.

Fertility

Non-clinical safety data are available regarding the effects of amifampridine on reproductive function. No impairment of fertility has been observed in non-clinical studies with amifampridine (see section 5.3).

4.7 Effects on ability to drive and use machines

Due to adverse reactions such as drowsiness, dizziness, seizures and blurred vision, amifampridine may have minor or moderate influence on the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Lambert-Eaton myasthenic syndrome is a very rare disorder. Consequently, there is little information on the adverse reactions of amifampridine treatment due to the small number of patients involved.

The most commonly reported adverse reactions are paraesthesias (such as peripheral and peribucal paraesthesias) and gastro-intestinal disorders (such as epigastralgia, diarrhoea, nausea and abdominal pain). The intensity and incidence of most adverse reactions is dose-dependent.

Table 1 below lists the adverse reactions reported with FIRDAPSE.

Tabulated list of adverse reactions

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000) and Unknown (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequencies were estimated based on a clinical study to evaluate the effects of amifampridine on cardiac repolarization at a single dose of 30 mg or 60 mg in healthy volunteers.

Table 1: Adverse Reactions Reported with FIRDAPSE

MedDRA System organ class	**MedDRA Preferred term**	**Frequency**
Psychiatric disorders:	Sleep disorders, anxiety	Unknown
Nervous system disorders:	Convulsions, chorea, myoclonia drowsiness, weakness, fatigue, headache	Unknown
	Dizziness[1], hypoaesthesia[1], paraesthesia[1]	Very common
Eye disorders:	Blurred vision	Unknown
Cardiac disorders:	Cardiac rhythm disorders, palpitations	Unknown
Vascular disorders:	Raynaud's syndrome	Unknown
	Cold extremities[1]	Common
Respiratory, thoracic and mediastinal disorders:	Bronchial hypersecretion, asthma attack in asthmatic patients or patients with a history of asthma, cough	Unknown
Gastrointestinal disorders:	Hypoaesthasia oral[1], paraesthesia oral[1], peripheral and peribucal paraesthesias, nausea[1]	Very common
	Abdominal pain	Common
	Diarrhoea, epigastralgia	Unknown
Hepatobiliary disorders:	Elevated liver enzyme levels (transaminases)	Unknown
Skin and subcutaneous disorders:	Hyperhidrosis[1], cold sweat[1]	Very common

[1] *Adverse reactions reported in a clinical study to evaluate the effects of amifampridine on cardiac repolarization at a single dose of 30 mg or 60 mg in healthy volunteers.*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is little experience with overdose. The manifestations of acute overdose include vomiting and abdominal pain. Patient should discontinue the treatment in the event of overdose. No specific antidote is known. Supportive care should be given as clinically indicated, including close monitoring of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX05.

Mechanism of action

Amifampridine blocks voltage-dependent potassium channels, thereby prolonging pre-synaptic cell membrane depolarisation. Prolonging the action potential enhances the transport of calcium into the nerve ending. The resulting increase in intra-cellular calcium concentrations facilitates exocytosis of acetylcholine-containing vesicles, which in turn enhances neuromuscular transmission.

It improves muscle strength and resting compound muscle action potential (CMAP) amplitudes with an overall weighted mean difference of 1.69 mV (95% CI 0.60 to 2.77).

Pharmacodynamic effects

The pharmacodynamic profile of amifampridine has been studied for a range of doses. A prospective, placebo-controlled, randomised study in 26 patients with Lambert-Eaton myasthenic syndrome (LEMS) reported clinical efficacy for amifampridine at the standard recommended maximum dose of 60 mg/day (Sanders *et al* 2000). Two further studies in a total of 57 patients with LEMS have reported data from higher doses of amifampridine. McEvoy *et al* 1989 reported data from a short-term study in 12 patients with LEMS, which demonstrated that administration of amifampridine at doses up to 100 mg/day for a period of 3 days was effective in treating the autonomic and motor symptoms of LEMS. Sanders *et al* 1998 presented data on efficacy and safety of amifampridine treatment at doses up to 100 mg/day in 45 patients with LEMS who were treated for an average of 31 months. Therefore, in exceptional circumstances higher doses up to a maximum of 80 mg/day may be of benefit when given with the appropriate safety monitoring. It is recommended that dose titration from 60 mg/day to 80 mg/day is performed in 5 mg increments every 7 days. Upward dose titration should be discontinued if any adverse event or ECG abnormality is observed.

The effect of a single dose of 30 mg or 60 mg of amifampridine phosphate was used to evaluate the pharmacokinetic-QTc relationship of amifampridine concentration on cardiac repolarization exposure in healthy volunteers. This evaluation was conducted in a Phase 1, double-blind, randomized, crossover study to define the ECG effects of amifampridine phosphate at these doses compared to placebo and moxifloxacin (a positive control) in healthy men and women who are slow acetylators (n=52). There was no effect of amifampridine phosphate on heart rate, atrioventricular conduction or cardiac depolarization as measured by the heart rate, PR and QRS interval durations. No subjects developed new clinically relevant ECG morphological changes following administration of amifampridine phosphate. No effect was observed of amifampridine phosphate on cardiac repolarization as assessed using the QTc interval.

This medicinal product has been authorised under ‘exceptional circumstances’.
This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency (EMA) will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Orally administered amifampridine is rapidly absorbed in humans, reaching peak plasma concentrations by 0.6 to 1.3 hours (mean values).

In humans, the rate and extent of absorption of amifampridine is influenced by food (See Table 2). There was a decrease in C_{max} and AUC, and an increase in the time to reach maximum plasma concentrations when amifampridine phosphate was administered with food as compared to without food. A 2-fold increase in the time to reach C_{max} (T_{max}) was observed in the presence of food. Similarly C_{max} and $AUC_{0-\infty}$ were greater in the fasted state than in the fed state. Overall, food slowed and decreased the absorption of amifampridine with a lowering of exposure by C_{max} on average by ~44% and lowered exposure by AUC ~20%. based on geometric mean ratios (fed-to-fasted).

Apparent plasma terminal elimination half-life differences were 3-4 fold between subjects in the food effect study. Bioavailability is approximately 93-100% based on recoveries of unmetabolised amifampridine and a major 3-N-acetylated amifampridine metabolite in urine.

Table 2: PK Parameters for Amifampridine in Fed and Fasted Subjects Following Administration of a Single Oral Dose of Amifampridine Phosphate

Amifampridine 20 mg	**C_{max} (ng/ml) mean (S.D.), range**	**$AUC_{0-\infty}$ (ng·hr/ml) Mean (S.D.), range**	**T_{max} (hr) mean(S.D.), range**	**$t_{1/2}$ (hr) mean (S.D.), range**
Fasted (N=45)	59.1 (34.4), 16-137	117 (76.6), 22.1-271	0.637 (0.247), 0.25-1.5	2.5 (0.73), 1.23-4.31
Fed* (N=46)	40.6 (31.3), 2.81-132	109 (76.4), 9.66-292	1.31 (0.88), 0.5-4.0	2.28 (0.704), 0.822-3.78

* Eating a standardised high-fat meal

In a study of healthy volunteers, systemic exposure of amifampridine was notably influenced by the overall metabolic acetylation activity of NAT enzymes and NAT2 genotype. The NAT genes are highly polymorphic and result in phenotypes with variable acetylation activity rates ranging from slow to fast. In the healthy volunteer study, fast acetylators were defined by having a caffeine metabolite ratio >0.3 and slow acetylators with a caffeine metabolite ratio <0.2 . There was significantly higher exposure to amifampridine in slow acetylators compared to fast acetylators. Statistically significant differences in amifampridine PK parameters C_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and apparent clearance was observed between fast and slow acetylators at all dose levels.

Table 3: Mean PK Parameters of Amifampridine in Healthy Subjects after Single Oral Doses (5-30mg) in Slow and Fast Acetylator Phenotypes

Amifampridine Dose (mg)	**5**		**10**		**20**		**30**	
Subjects (N)	6	6	6	6	6	6	6	6
Acetylator Phenotype	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
Mean Amifampridine PK Parameters								
AUC_{0-t} (ng·hr/ml)	2.89	30.1	9.55	66.3	24.7	142	43.5	230
$AUC_{0-\infty}$ (ng·hr/ml)	3.57	32.1	11.1	68.9	26.2	146	45.2	234
C_{max} (ng/ml)	3.98	17.9	9.91	34.4	16.2	56.7	25.5	89.6
T_{max} (hr)	0.750	0.830	0.805	1.14	1.04	1.07	0.810	1.29
$t_{1/2}$ (hr)	0.603	2.22	1.21	2.60	1.23	2.93	1.65	3.11

The mean caffeine acetylator ratio for these 12 subjects receiving four escalating doses were 0.408 and 0.172 for fast and slow acetylators types respectively.

Distribution

Distribution of amifampridine was studied in the rat. Following oral administration of radiolabelled [14C] amifampridine, radioactive material is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body. Concentrations in tissues are generally similar to or greater than concentrations in plasma, with the greatest concentration in organs of excretion (liver, kidney and the gastrointestinal tract) and some tissues of glandular function (lacrimal, salivary, mucous, pituitary and thyroid glands).

Biotransformation

In vitro and *in vivo* studies in humans indicate that amifampridine is metabolised to a single major 3-N-acetylated amifampridine metabolite.

Elimination

In humans, 93.2% to 100% of amifampridine is excreted into the urine within 24 hours after dosing as amifampridine (19%) and its 3-N-acetylated amifampridine metabolite (74.0% to 81.7%). The plasma elimination half-life is approximately 2.5 hours for the amifampridine and 4 hours for the 3-N-acetylated amifampridine metabolite.

The overall clearance of amifampridine is predominantly due to metabolism by N-acetylation and acetylator phenotype has a greater effect on an individual's metabolism and elimination of amifampridine than does elimination by renal function (See Table 4).

Renal impairment

Exposure of amifampridine was generally higher in subjects with renal impairment than in subjects with normal renal function; however, NAT2 phenotype had a greater effect on an individual's exposure to amifampridine than renal function status (See Table 4). Amifampridine exposure by $AUC_{0-\infty}$ was up to 2-fold higher in slow acetylators and up to 3-fold higher in fast acetylators with severe renal impairment compared to subjects with normal renal function. Exposure by C_{max} was marginally affected by renal impairment regardless of acetylation status.

In contrast, the 3-N-acetyl metabolite exposure levels were affected to a greater extent by renal impairment than those for amifampridine. The 3-N-acetyl metabolite exposure by $AUC_{0-\infty}$ was up to 6.8-fold higher in slow acetylators and up to 4-fold higher in fast acetylators with severe renal impairment compared to subjects with normal renal function. Exposure by C_{max} was only marginally affected by renal impairment regardless of acetylation status. Although the metabolite is inactive at potassium channels, potential off target effects due to accumulation are unknown.

Table 4: Mean PK Parameters of Amifampridine in Normal and Renal Impaired Subjects after Single Oral Dose Administration (10mg) in Slow and Fast Acetylator Phenotypes

Renal Status	Normal		Mild		Moderate		Severe	
Subjects (N)	4	4	4	4	4	4	4	4
NAT2 Phenotype	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
Mean Amifampridine PK Parameters								
$AUC_{0-\infty}$ (ng·h/ml)	10.7	59.1	16.1	81.3	14.3	126	32.8	119
C_{max} (ng/ml)	7.65	38.6	11.1	33.5	8.33	52.5	9.48	44.1
T_{max} (hr)	0.44	0.43	0.88	0.88	0.51	0.55	0.56	0.63
$t_{1/2}$ (hr)	1.63	2.71	1.86	2.95	1.72	3.89	1.64	3.17
Mean 3-N-acetyl Amifampridine PK Parameters								
$AUC_{0-\infty}$ (ng·h/ml)	872	594	1264	1307	2724	1451	3525	4014
C_{max} (ng/ml)	170	115	208	118	180	144	164	178
T_{max} (hr)	1.13	0.75	1.44	1.38	2.00	1.13	1.63	2.81
$t_{1/2}$ (hr)	4.32	4.08	5.35	7.71	13.61	6.99	18.22	15.7

Hepatic impairment

There are no data on the pharmacokinetics of amifampridine in patients with hepatic impairment (see sections 4.2 and 4.4).

Paediatric population

There are no data on the pharmacokinetics of amifampridine in paediatric patients (see sections 4.2).

The effect of age on the pharmacokinetics of amifampridine has not been studied.

5.3 Preclinical safety data

In safety pharmacology studies in rats, no respiratory system related effects were seen up to 10 mg/kg or on the central nervous system up to 40 mg/kg.

In a repeat-dose toxicity studies in rats and dogs, effects on the central and autonomic nervous system, increased liver and kidney weights and cardiac effects (second degree atrioventricular block) were seen. No safety margins to human exposure were achieved in the animal studies due to the sensitivity of the animal models used.

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 is unknown.

Amifampridine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests.

Animal studies evaluating the reproductive and developmental toxicity of amifampridine were conducted in rats and rabbits at doses up to 75 mg/kg/day. Amifampridine had no adverse reaction on male or female fertility in rats at doses up to 75 mg/kg/day, and no effect on post-natal development or fertility was observed in the offspring of the treated animals. In a perinatal/postnatal reproduction study in pregnant rats treated with amifampridine, a dose-related increase in the percentage of mothers with stillborn offspring (16.7%-20%) was observed at 22.5 mg/kg/day and 75 mg/kg/day (1.1 and 2.7 times the 80 mg per day dose in humans based on C_{max}). However, in a similar study in pregnant rabbits, there was no effect on embryo-foetal viability when evaluated just prior to birth at doses up to 57 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Anhydrous colloidal silica
Calcium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Perforated unit dose thermoformed blisters (Thermoformed aluminium-PVC/PVDC laminate sheets) containing 10 tablets.

One box contains 100 tablets comprising 10 strips with 10 tablets each.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/601/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 December 2009
Date of latest renewal: 1 December 2014

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

EXCELLA GmbH & Co. KG
Nürnberger Strasse 12
90537 Feucht
Germany

BioMarin International Limited
Shanbally, Ringaskiddy, Co. Cork
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
To establish a Lambert Eaton Patient Registry as defined in the RMP and also incorporating measures of efficacy.	Annual reports: as part of the annual re-assessment dossier

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

FIRDAPSE 10 mg tablets
amifampridine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amifampridine phosphate equivalent to 10 mg of amifampridine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

Store in the original blister in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/601/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FIRDAPSE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Perforated unit dose thermoformed blisters

1. NAME OF THE MEDICINAL PRODUCT

FIRDAPSE 10 mg tablets
amifampridine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

FIRDAPSE 10 mg tablets
amifampridine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What FIRDAPSE is and what it is used for
2. What you need to know before you take FIRDAPSE
3. How to take FIRDAPSE
4. Possible side effects
5. How to store FIRDAPSE
6. Contents of the pack and other information

1. What FIRDAPSE is and what it is used for

FIRDAPSE is used to treat symptoms of a disease of the nerves and the muscles called Lambert-Eaton myasthenic syndrome or LEMS in adults. This disease is a disorder affecting the transmission of nerve impulses to muscles, resulting in muscle weakness. It can be associated with certain tumour types (paraneoplastic form of LEMS) or in the absence of these tumours (non-paraneoplastic form of LEMS).

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.

2. What you need to know before you take FIRDAPSE

Do not take FIRDAPSE

- If you are allergic to amifampridine, or any of the other ingredients of this medicine (listed in section 6)
- If you have uncontrolled asthma
- If you are epileptic
- Together with medicines that may change the electrical activity of your heart (QT-interval prolongation - detectable in the electrocardiogram), such as:
    - Sultopride (a medicine prescribed to treat certain behavioural disorders in adults),
    - Antiarrhythmic medicine (e.g., disopyramide)

    - Medicines to treat digestive problems (e.g., cisapride, domperidone)
    - Medicines to treat infections - antibiotics (e.g., rifampicin) and antifungals (e.g., ketoconazole)
- Together with medicines with a therapeutic dose close to the maximum safe dose
- If you were born with heart problems (congenital QT syndromes)

If you have any doubts, ask your doctor or pharmacist for advice.

Warnings and precautions
Talk to your doctor or pharmacist before taking FIRDAPSE.

Tell your doctor if you have
- Asthma
- A history of fits (convulsions)
- Kidney problems
- Liver problems

Your doctor will monitor carefully how FIRDAPSE works for you and may need to change the dose of the medicines you take. Your doctor will also monitor your heart at the start of your treatment and also every year thereafter.

If you have LEMS but do not have cancer, your doctor will make a thorough assessment of the potential risk of cancer with FIRDAPSE before commencing treatment.

Tell any physician you consult that you are using FIRDAPSE.

Stop the treatment and immediately consult your doctor in the event of:
- Fits (convulsions)
- Asthma

Other medicines and FIRDAPSE
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some medicines may interact with FIRDAPSE when taken together. The following medicines must not be combined with FIRDAPSE:
- Medicines that may change the electrical activity of your heart (QT-interval prolongation - detectable in the electrocardiogram) e.g., sultopride, disopyramide, cisapride, domperidone, rifampicin, and ketoconazole (see “Do not take FIRDAPSE”)

It is especially important to talk to your doctor if you are taking one of the following medicines or plan to start taking the following medications:
- Medicines for malaria (e.g. halofantrine and mefloquine)
- Tramadol (a painkiller)
- Antidepressants - tricyclic antidepressants (e.g. clomipramine, amoxapine), selective serotonin reuptake inhibitors (e.g. citalopram, dapoxetine) and atypical antidepressants (e.g. buproprion)
- Medicines for mental problems (e.g. haloperidol, carbamazapine, chlorpromazine, clozapine)
- Medicines to treat Parkinson's disease - anticholinergics (e.g. trihexylphenidyl, mesylate), MAO-B inhibitors (e.g. selegiline, deprenyl), COMT inhibitors (e.g. entacapone)
- Medicines to treat allergies - antihistamines (e.g. terfenadine, astemizole, cimetidine)
- Medicines to relax your muscles - (e.g. mivacurium, pipercurium, suxamethonium)
- Sedatives (e.g. barbiturates)

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

FIRDAPSE should not be used if you are pregnant. You must use effective contraception throughout the treatment. If you discover that you are pregnant during the treatment, inform your doctor immediately.

It is not known whether FIRDAPSE is excreted in human breast milk. You and your doctor should discuss the risks and benefits of continuing to take FIRDAPSE while breastfeeding.

Driving and using machines
This medicine may cause drowsiness, dizziness, fits (convulsions) and blurred vision, which may affect your ability to drive or use machines. Do not drive or operate machines if you experience these side effects.

3. How to take FIRDAPSE

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The dose you should take is established by your doctor based on the intensity of your symptoms and certain genetic factors. This dose suits you only.

The starting dose is 5 mg amifampridine (half a tablet) three times daily (i.e. 15 mg per day). Your doctor may increase this dose slowly first to 5 mg (half a tablet) four times daily (i.e. 20 mg per day). Then your doctor may continue to increase your total daily dose adding 5 mg (half a tablet) per day, every 4 or 5 days.

The maximum recommended dose is 60 mg per day (i.e. a total of six tablets to be taken at intervals during the day). Total daily doses above 20 mg should be divided into two to four separate doses. No single dose should exceed 20 mg (two tablets).

The tablets have a score-line to allow them to be broken in half. The tablets should be swallowed with some water and are to be taken with food.

Patients with liver/kidney problems:
FIRDAPSE should be used with caution in patients with liver or kidney problems. A starting dose of 5 mg (half tablet) FIRDAPSE daily is recommended in patients with moderate or severe liver or kidney problems. For patients with mild liver or kidney problems a starting dose of 10 mg (5 mg twice a day) FIRDAPSE daily is recommended. For these patients the dose of FIRDAPSE should be increased more slowly than in those without liver or kidney problems with doses increased in 5 mg increments every 7 days. If any side effects occur, please consult your doctor as you may need to stop increasing the dose.

If you take more FIRDAPSE than you should
If you take more FIRDAPSE than you should have, you may suffer from vomiting or a stomach ache. If you experience any of these symptoms, you should contact your doctor or pharmacist immediately.

If you forget to take FIRDAPSE
If you forget to take FIRDAPSE, do not take a double dose to make up for the dose you have forgotten but continue to take your treatment as prescribed by your doctor.

If you stop taking FIRDAPSE
If the treatment is stopped, you may experience symptoms such as tiredness, slow reflexes and constipation. Do not stop treatment without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop the treatment and immediately consult your doctor in the event of:
- Fits (convulsions)
- Asthma

Very common side effects which may affect more than 1 in 10 people are:
- Tingling and numbness around the mouth and extremities (such as feet and hands)
- Reduced sense of touch or sensation
- Nausea
- Dizziness
- Increase sweating, cold sweat

Common side effects which may affect up to 1 in 10 people are:
- Stomach ache
- Cold hands and feet

Other side effects are:
The intensity and incidence of most side effects depends on the dose you are taking. The following side effects have also been reported (frequencies cannot be estimated from the available data):
- Raynaud's syndrome (circulation disorder affecting the fingers and toes)
- Diarrhoea
- Fits (convulsions)
- Cough, excessive or viscous mucus in the breathing passage, asthma attack in asthmatic patients or patients with a history of asthma
- Blurred vision
- Heart rhythm disorders, fast or irregular heartbeats (palpitations)
- Weakness, tiredness, headache
- Anxiety, sleep disorders, drowsiness
- Chorea (movement disorder), myoclonia (muscle spasm or twitching)
- Increase in certain liver enzymes (transaminases) seen on blood tests

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FIRDAPSE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C. Store in the original package, in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What FIRDAPSE contains

- The active substance is amifampridine. Each tablet contains amifampridine phosphate equivalent to 10 mg of amifampridine.
- The other ingredients are microcrystalline cellulose, anhydrous colloidal silica and calcium stearate.

What FIRDAPSE looks like and contents of the pack

White, round tablet, flat-faced on one side and scored on the other side.
The tablets can be divided into equal halves.
Perforated unit dose thermoformed blisters (Thermoformed aluminium-PVC/PVDC laminate sheets) containing 10 tablets.
One box contains 100 tablets comprising 10 strips with 10 tablets each.

Marketing Authorisation Holder

BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

Manufacturers

EXCELLA GmbH & Co. KG
Nürnberger Strasse 12
90537 Feucht
Germany

BioMarin International Limited
Shanbally, Ringaskiddy, Co. Cork
Ireland

This leaflet was last revised in MM/YYYY

This medicine has been authorised under “Exceptional Circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Annex IV

Grounds for one additional renewal

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Firdapse remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

Firdapse was authorised under exceptional circumstances and two specific obligations, both linked to safety, are still outstanding, i.e. the patient registry and the carcinogenicity studies.

Furthermore, in terms of exposure, the CHMP considered that the safety data available through the Lambert-Eaton myasthenic syndrome (LEMS) registry since the granting of the initial marketing authorisation were limited, as only 37 subjects recruited to the registry are on Firdapse. The registry is planned to be continued until at least 70 patients are recruited on Firdapse and followed for up to five years, with a minimum of at least three years for the last subject recruited to the registry.

The CHMP also considered that although Firdapse is marketed in most EU member states, the size of the patient population is limited, resulting in limitations of the overall exposure to the product. In addition, the CHMP recognised that pharmacy preparations of amifampridine are still being used, which further limits the numbers of patients treated with Firdapse.

Based on these issues, the CHMP was of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.

The MAH should continue to submit yearly PSURs, until otherwise specified by the CHMP.