ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications


4.2 Posology and method of administration

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

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. 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 Firdapse in the fed and fasted state.

Genetic differences can account for the variable systemic exposure of Firdapse, for further information please see section 4.4 and section 5.2.

For oral use only.

Paediatric and adolescent patients

FIRDAPSE is not recommended for use in this patient group aged below 18 years due to a lack of data on safety and efficacy (see section 5.2).

Patients with renal or hepatic impairment

FIRDAPSE should be used with caution in patients with renal or hepatic impairment. A starting dose of 5 mg FIRDAPSE 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 FIRDAPSE 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).
4.3 **Contraindications**

- Hypersensitivity to the active substance, or to any of the excipients
- 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**

No studies have been conducted in patients with renal or 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).

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.

Amifampridine has not been fully tested in carcinogenicity models, and the carcinogenicity risk associated with treatment has not been determined. The use of amifampridine in patients with the non-paraneoplastic form of LEMS should only be commenced following a thorough assessment of the risk-benefit to the patient.

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.

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.

The pharmacokinetics and systemic exposure to amifampridine is notably influenced by the overall metabolic acetylation activity of n-acetyl-transferase (NAT) enzymes 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 N-acetyltransferases (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 drugs. 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 FIRDAPSE, the concomitant use with sulotrope 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 FIRDAPSE 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**

No adequate clinical data on exposed pregnancies are available for amifampridine. No non-clinical safety data are available regarding the effects of amifampridine on reproductive function (see section 5.3).

FIRDAPSE should not be used during pregnancy.

Both men and women of childbearing potential must use effective contraception during FIRDAPSE treatment.

It is unknown whether amifampridine is excreted in human breast milk. The excretion of amifampridine in milk has not been studied in animals. FIRDAPSE should not be used during breast-feeding.

4.7 **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, due to adverse reactions such as drowsiness, dizziness, seizures and blurred vision, FIRDAPSE may have minor or moderate influence on the ability to drive or use machines (see section 4.8).

4.8 **Undesirable effects**

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 in the published literature 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.

The following adverse reactions have also been reported:

- Psychiatric disorders: Sleep disorders, anxiety
- Nervous system disorders: Convulsions, drowsiness, dizziness, weakness, fatigue, headache, chorea, myoclonia
- Eye disorders: Blurred vision
- Cardiac disorders: Cardiac rhythm disorders, palpitations
- Vascular disorders: Raynaud's syndrome, cold extremities
- Respiratory, thoracic and mediastinal disorders: Cough, bronchial hypersecretion, asthma attack in asthmatic patients or patients with a history of asthma
- Hepatobiliary disorders: Elevated liver enzyme levels (transaminases)

Given the very limited data available it is not possible to estimate the frequencies of individual adverse reactions.

4.9 **Overdose**

There is little experience with overdose. Since the effects are dose dependent, the manifestations of acute overdose are expected to include general weakness combined with diffuse paraesthesias, nausea, vomiting, convulsions and cardiac rhythm disorders. 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 and cardiac status of the patient.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system medicinal products ATC code: N07XX05.

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).

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.

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 1 below for information on PK parameters of amifampridine in healthy volunteers. There was a decrease in C<sub>max</sub> and AUC, and a longer T<sub>max</sub> (2 fold) when amifampridine phosphate was administered with food as compared to without food. Based on the PK parameter ranges given in Table 1 a C<sub>max</sub> range from 16 - 137 ng/mL is seen in the fasted state and a range from 2.81 – 132 is seen in the fed state. Similarly for AUC<sub>0-∞</sub> range from 22.1 – 271 ng-hr/mL is seen in the fasted state and a range from 9.66 – 292 ng-hr/mL is seen in the fed state.

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 drug and a major 3-N-acetylated amifampridine metabolite in urine.

Table 1: PK Parameters for Amifampridine in Fed and Fasted Subjects Following Administration of a Single Oral Dose of Amifampridine Phosphate

| Amifampridine 20 mg | C<sub>max</sub> (ng/mL) mean (S.D.), range | AUC<sub>0-∞</sub> (ng-hr/mL) Mean (S.D.), range | T<sub>max</sub> (hr) mean(S.D.), range | t<sub>1/2</sub> (hr) mean (S.D.), range |
### Table 2: Mean Firdapse PK Parameters of Amifampridine in Healthy Subjects after Single Oral Doses (5-30mg) in Slow and Fast Acetylator Phenotypes

<table>
<thead>
<tr>
<th>Amifampridine Dose (mg)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (N)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Acetylator Phenotype</td>
<td>Fast</td>
<td>Slow</td>
<td>Fast</td>
<td>Slow</td>
</tr>
<tr>
<td>Mean Amifampridine PK Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL) mean (S.D.), range</td>
<td>79.1 (34.1), 31 - 167</td>
<td>117 (76.6), 22.1 - 271</td>
<td>0.637 (0.247), 0.25 – 1.5</td>
<td>2.5 (0.73), 1.23 – 4.31</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng*h/mL) mean (S.D.), range</td>
<td>3.57 (32.1), 31 - 167</td>
<td>117 (76.6), 22.1 - 271</td>
<td>0.637 (0.247), 0.25 – 1.5</td>
<td>2.5 (0.73), 1.23 – 4.31</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr) mean (S.D.), range</td>
<td>1.31 (0.88), 0.5 – 4.0</td>
<td>1.31 (0.88), 0.5 – 4.0</td>
<td>1.31 (0.88), 0.5 – 4.0</td>
<td>1.31 (0.88), 0.5 – 4.0</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr) mean (S.D.), range</td>
<td>2.28 (0.704), 0.822 – 3.78</td>
<td>2.28 (0.704), 0.822 – 3.78</td>
<td>2.28 (0.704), 0.822 – 3.78</td>
<td>2.28 (0.704), 0.822 – 3.78</td>
</tr>
</tbody>
</table>

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 radiolabeled $[^{14}C]$ 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 parent drug (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 parent drug and 4 hours for the 3-N-acetylated amifampridine metabolite.

**Special populations:**
There are no data on the pharmacokinetics of amifampridine in paediatric patients and patients with renal or hepatic impairment (see sections 4.2 and 4.4).

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

5.3 Preclinical safety data

Only limited preclinical data for amifampridine are available.

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

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

No long-term toxicity studies of more than a 4 weeks duration have been conducted.

Amifampridine was not genotoxic in a standard battery of in vitro and in vivo tests, but the results of full carcinogenicity studies are not available.

No reproductive toxicity or carcinogenicity studies have been performed.

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
164 Shaftesbury Avenue
London, WC2H 8HL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/601/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 December 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.ema.europa.eu
ANNEX II

A. MANUFACTURING AUTHORIZATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORIZATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORIZATION HOLDER

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORIZATION MEASURES FOR THE MARKETING AUTHORIZATION UNDER EXCEPTIONAL CIRCUMSTANCES
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

ETABLISSEMENT PHARMACEUTIQUE DE L'AP-HP (ASSISTANCE PUBLIQUE-HOPITAUX DE PARIS)
AGEPS
7, rue du Fer à Moulin
F-75005 Paris
France

Catalent UK Packaging Ltd.
Wingates Industrial Park,
Westhoughton, Bolton,
Lancs, BL5 3XX
United Kingdom

EXCELLA GmbH
Nürnberger Strasse 12
90537 Feucht
Germany

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 OF THE MARKETING AUTHORIZAION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

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

Not applicable

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

• Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any agreed subsequent updates of the RMP

An updated RMP shall be submitted annually until renewal.
When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.
In addition, 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:

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the continuous reassessment of the benefit/risk profile.

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>To perform a thorough QT/QTC study in healthy volunteers in line with ICH E14 guidelines.</td>
<td>Final study report: December 2013</td>
</tr>
<tr>
<td>To establish a Lambert Eaton Patient Registry as defined in the RMP and also incorporating measures of efficacy.</td>
<td>Annual reports: as part of the annual reassessment dossier</td>
</tr>
<tr>
<td>To perform carcinogenicity testing in an appropriate model.</td>
<td>Final study report: June 2016</td>
</tr>
</tbody>
</table>
ANNEX III

LABELLING AND PACKAGE LEAFLET
A: LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>FIRDAPSE 10 mg tablets</td>
</tr>
<tr>
<td>amifampridine</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>Each tablet contains amifampridine phosphate</td>
</tr>
<tr>
<td>equivalent to 10 mg of amifampridine.</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>100 tablets</td>
</tr>
<tr>
<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST</td>
</tr>
<tr>
<td>BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td>Do not store above 30°C.</td>
</tr>
<tr>
<td>Store in the original blister in order to protect from light and moisture.</td>
</tr>
</tbody>
</table>
### 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  
164 Shaftesbury Avenue  
London, WC2H 8HL  
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/601/001

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

FIRDAPSE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Perforated unit dose thermoformed blisters

1. NAME OF THE MEDICINAL PRODUCT

FIRDAPSE 10 mg
amifampridine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
B: PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.
• 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What FIRDAPSE is and what it is used for
2. Before you take FIRDAPSE
3. How to take FIRDAPSE
4. Possible side effects
5. How to store FIRDAPSE
6. Further 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. BEFORE YOU TAKE FIRDAPSE

Do not take FIRDAPSE
• If you are allergic (hypersensitive) to amifampridine, or any of the other ingredients of FIRDAPSE,
• If you have uncontrolled asthma,
• If you are epileptic,
• In combination with sultopride (a medicine prescribed to treat certain behavioural disorders in adults),
• In combination with medicines that may change the electrical activity of your heart (QT-interval prolongation - detectable in the electrocardiogram),
• In combination 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.

Take special care with 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

Taking other medicines
You may need to take special precautions or change your dose of FIRDAPSE if you are taking FIRDAPSE with some other medicines. It is especially important to mention to your doctor if you are taking one of the following medicines:
• Medicines for malaria (e.g. halofantrine and mefloquine)
• Disopyrimide (an antiarrhythmic medication)
• 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. trihexyphenidyl, 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 treat digestive problems (e.g. cisapride, domperidone)
• Medicines to treat infections - antibiotics (e.g. rifampicin) and antifungals (e.g. ketoconazole)
• 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
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.

You should not breastfeed whilst taking this medicinal product.

Ask your pharmacist or doctor for advice before taking any medicine.

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 FIRDAPSE 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 (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 FIRDAPSE is recommended in patients with moderate or severe impairment of liver or kidney function. For patients with mild impairment of liver or kidney function a starting dose of 10 mg FIRDAPSE 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 adverse events 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 feel weak, nauseous, and experience mild tingling or numbness in part of your body. Depending on how much FIRDAPSE you have taken, you may also suffer from convulsions, vomiting or problems with your heart (cardiac rhythm disorders). 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 product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

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

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

**The most commonly reported side effects are:**
- Tingling and numbness around the mouth and extremities (such as feet and hands),
- Stomach ache, diarrhoea, feeling sick and abdominal pain.

**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):
- Fits (convulsions),
- Cough, excessive or viscous mucus in the breathing passage, asthma attack in asthmatic patients or patients with a history of asthma,
• Raynaud’s syndrome (circulation disorder affecting the fingers and toes), cold hands and feet,
• Blurred vision,
• Heart rhythm disorders, fast or irregular heartbeats, also called palpitations,
• Weakness, tiredness, headache,
• Anxiety, dizziness, sleep disorders, drowsiness,
• Chorea (movement disorder), myoclonia (muscle spasm or twitching),
• Increase in certain liver enzymes (transaminases) seen on blood tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FIRDAPSE

Keep out of the reach and sight of children.

Do not use 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER 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, flat-faced and scored tablet on one face.
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 and Manufacturer

Marketing Authorisation Holder:
BioMarin Europe Limited
164 Shaftesbury Avenue
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United Kingdom

Manufacturers:

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This leaflet was last approved 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 (EMA) 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 (EMA) web site: http://www.ema.europa.eu