ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fampridine Accord 10 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg of fampridine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off white, oval shaped, biconvex, bevel-edged, film coated tablets, approximately 13.1 x 8.1 mm in dimensions, debossed with 'FH6' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fampridine Accord is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability (EDSS 4-7).

4.2 Posology and method of administration

Treatment with fampridine is restricted to prescription and supervision by physicians experienced in the management of MS.

Posology

The recommended dose is one 10 mg tablet, twice daily, taken 12 hours apart (one tablet in the morning and one tablet in the evening). Fampridine should not be administered more frequently or at higher doses than recommended (see section 4.4). The tablets should be taken without food (see section 5.2).

Missed dose

The usual dosing regimen should always be followed. A double dose should not be taken if a dose is missed.

Starting and evaluating Fampridine Accord treatment

- Initial prescription should be limited to two to four weeks of therapy as clinical benefits should generally be identified within two to four weeks after starting Fampridine Accord.
- An assessment of walking ability, e.g. the Timed 25 Foot Walk (T25FW) or Twelve Item Multiple Sclerosis Walking Scale (MSWS-12), is recommended to evaluate improvement within two to four weeks. If no improvement is observed, the treatment should be discontinued
- This medicinal product should be discontinued if benefit is not reported by patients.

Re-evaluating Fampridine Accord treatment

If decline in walking ability is observed, physicians should consider an interruption to treatment in order to reassess the benefits of fampridine (see above). The re-evaluation should include withdrawal of this medicinal product and performing an assessment of walking ability. Fampridine should be discontinued if patients no longer receive walking benefit.

Special populations

Elderly Renal function should be checked in the elderly before starting treatment with this medicinal product. Monitoring renal function to detect any renal impairment is recommended in the elderly (see section 4.4).

Patients with renal impairment
Fampridine is contraindicated in patients with moderate and severe renal impairment (creatinine clearance < 50 mL/min) (see sections 4.3 and 4.4).

Patients with hepatic impairment
No dose adjustment is required for patients with hepatic impairment.

Paediatric population
The safety and efficacy of this medicinal product in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Fampridine Accord is for oral use.

The tablet must be swallowed whole. It must not be divided, crushed, dissolved, sucked or chewed.

4.3 Contraindications

Hypersensitivity to fampridine or to any of the excipients listed in section 6.1.

Concurrent treatment with other medicinal products containing fampridine (4-aminopyridine).

Patients with prior history or current presentation of seizure.

Patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Concomitant use of Fampridine Accord with medicinal products that are inhibitors of Organic Cation Transporter 2 (OCT2) for example, cimetidine.

4.4 Special warnings and precautions for use

Seizure risk

Treatment with fampridine increases seizure risk (see section 4.8).

This medicinal product should be administered with caution in the presence of any factors which may lower seizure threshold.

Fampridine should be discontinued in patients who experience a seizure while on treatment.

Renal impairment

Fampridine is primarily excreted unchanged by the kidneys. Patients with renal impairment have higher plasma concentrations which are associated with increased adverse reactions, in particular neurological effects. Determining renal function before treatment and its regular monitoring during treatment is recommended in all patients (particularly in the elderly in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.

Caution is required when Fampridine Accord is prescribed in patients with mild renal impairment or in patients using medicinal products that are substrates of OCT2 for example, carvedilol, propranolol and metformin.

Hypersensitivity reactions

In post-marketing experience, serious hypersensitivity reactions (including anaphylactic reaction) have been reported, the majority of these cases occurred within the first week of treatment. Particular attention should be given to patients with a previous history of allergic reactions. If an anaphylactic or other serious allergic reaction occurs, this medicinal product should be discontinued and not restarted.

Other warnings and precautions

Fampridine should be administered with caution to patients with cardiovascular symptoms of rhythm and sinoatrial or atrioventricular conduction cardiac disorders (these effects are seen in overdose). There is limited safety information in these patients.

The increased incidence of dizziness and balance disorder seen with fampridine may result in an increased risk of falls. Therefore, patients should use walking aids as needed.

In clinical studies low white blood cell counts were seen in 2.1% of fampridine patients versus 1.9% of patients on placebo. Infections were seen in the clinical studies (see section 4.8) and increased infection rate and impairment of the immune response cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Concurrent treatment with other medicinal products containing fampridine (4-aminopyridine) is contraindicated (see section 4.3).

Fampridine is eliminated mainly via the kidneys with active renal secretion accounting for about 60% (see section 5.2). OCT2 is the transporter responsible for the active secretion of fampridine. Thus, the concomitant use of fampridine with medicinal products that are inhibitors of OCT2 for example, cimetidine are contraindicated (see section 4.3) and concomitant use of fampridine with medicinal products that are substrates of OCT2 for example, carvedilol, propranolol and metformin is cautioned (see section 4.4.)

Interferon: fampridine has been administered concomitantly with interferon-beta and no pharmacokinetic medicinal product interactions were observed.

Baclofen: fampridine has been administered concomitantly with baclofen and no pharmacokinetic medicinal product interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of fampridine in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure it is preferable to avoid the use of fampridine in pregnancy.

Breast-feeding

It is unknown whether fampridine is excreted in human or animal milk. Fampridine Accord is not recommended during breast-feeding.

Fertility

In animal studies no effects on fertility were seen.

4.7 Effects on ability to drive and use machines

Fampridine Accord has a moderate influence on the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of fampridine has been evaluated in randomised controlled clinical studies, in open label long term studies and in the post marketing setting.

Adverse reactions identified are mostly neurological and include seizure, insomnia, anxiety, balance disorder, dizziness, paraesthesia, tremor, headache and asthenia. This is consistent with fampridine's pharmacological activity. The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with fampridine given at the recommended dose, are reported as urinary tract infection (in approximately 12 % of patients).

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency category
Infections and infestations	Urinary tract infection[1] Influenza[1] Nasopharyngitis[1] Viral infection[1]	Very Common Common Common Common
Immune system disorders	Anaphylaxis Angioedema Hypersensitivity	Uncommon Uncommon Uncommon
Psychiatric disorders	Insomnia Anxiety	Common Common
Nervous system disorders	Dizziness Headache Balance disorder Vertigo Paraesthesia Tremor Seizure[2] Trigeminal neuralgia[3]	Common Common Common Common Common Common Uncommon Uncommon
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular disorders	Hypotension[4]	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea Pharyngolaryngeal pain	Common Common
Gastrointestinal disorders	Nausea Vomiting Constipation Dyspepsia	Common Common Common Common
Skin and subcutaneous tissue disorders	Rash Urticaria	Uncommon Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Asthenia Chest discomfort[4]	Common Uncommon

[1] See section 4.4
[2] See sections 4.3 and 4.4
[3] Includes both de novo symptoms and exacerbation of existing trigeminal neuralgia
[4] These symptoms were observed in the context of hypersensitivity

Description of selected adverse reactions

Hypersensitivity

In post-marketing experience, there have been reports of hypersensitivity reactions (including anaphylaxis) which have occurred with one or more of the following: dyspnoea, chest discomfort, hypotension, angioedema, rash and urticaria. For further information on hypersensitivity reactions, please refer to sections 4.3 and 4.4.

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

Symptoms

Acute symptoms of overdose with fampridine were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia.

Central nervous system adverse reactions at high doses of 4-aminopyridine include dizziness, confusion, seizures, status epilepticus, involuntary and choreoathetoid movements. Other side effects at high doses include cases of cardiac arrhythmias (for example, supraventricular tachycardia and bradycardia) and ventricular tachycardia as a consequence of potential QT prolongation. Reports of hypertension have also been received.

Management

Patients who overdose should be provided supportive care. Repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX07.

Pharmacodynamic effects

Fampridine is a potassium channel blocker. By blocking potassium channels, fampridine reduces the leakage of ionic current through these channels, thereby prolonging repolarization and thus enhancing action potential formation in demyelinated axons and neurological function. Presumably, by enhancing action potential formation, more impulses might be conducted in the central nervous system.

Clinical efficacy and safety

Three phase III, randomised, double-blind, placebo controlled confirmatory studies, (MS-F203 and MS-F204 and 218MS305) have been performed. The proportion of responders was independent of concomitant immunomodulatory therapy (including interferons, glatiramer acetate, fingolimod and natalizumab). The fampridine dose was 10 mg twice a day (BID).

Studies MS-F203 and MS-F204

The primary endpoint in studies MS-F203 and MS-F204 was the responder rate in walking speed as measured by the Timed 25-foot Walk (T25FW). A responder was defined as a patient who consistently had a faster walking speed for at least three visits out of a possible four during the double blind period as compared to the maximum value among five off-treatment visits.

A significantly greater proportion of fampridine treated patients were responders as compared to placebo (MS-F203: 34.8% vs. 8.3%, $p< 0.001$; MS-F204: 42.9% vs. 9.3%, $p< 0.001$).

Patients who responded to fampridine increased their walking speed on average by 26.3% vs 5.3% on placebo ($p< 0.001$) (MS-F203) and 25.3% vs 7.8% ($p< 0.001$) (MS-F204). The improvement appeared rapidly (within weeks) after starting the treatment.

Statistically and clinically meaningful improvements in walking were seen, as measured by the 12-item Multiple Sclerosis Walking Scale.

Table 2: Studies MS-F203 and MS-F204

STUDY *	**MS-F203**		**MS-F204**	
	Placebo	**Fampridine 10 mg BID**	**Placebo**	**Fampridine 10 mg BID**
n of subjects	72	224	118	119
Consistent improvement	**8.3%**	**34.8%**	**9.3%**	**42.9%**
Difference		**26.5%**		**33.5%**
$CI_{95\%}$		17.6%, 35.4%		23.2%, 43.9%
P-value		< 0.001		< 0.001
≥ 20% improvement	11.1%	31.7%	15.3%	34.5%
Difference		20.6%		19.2%
$CI_{95\%}$		11.1%,30.1%		8.5%,29.9%
P-value		< 0.001		< 0.001
Walking speed Feet/sec	Ft per sec	Ft per sec	Ft per sec	Ft per sec
Baseline	2.04	2.02	2.21	2.12
Endpoint	2.15	2.32	2.39	2.43
Change	0.11	0.30	0.18	0.31
Difference	0.19		0.12	
p-value	0.010		0.038	
Average % change	5.24	13.88	7.74	14.36
Difference	8.65		6.62	
p-value	< 0.001		0.007	
MSWS-12-score (mean, sem)				
Baseline	69.27 (2.22)	71.06 (1.34)	67.03 (1.90)	73.81 (1.87)
Average change	-0.01 (1.46)	-2.84 (0.878)	0.87 (1.22)	-2.77 (1.20)
Difference	2.83		3.65	
p-value	0.084		0.021	
LEMMT (mean, sem) (Lower Extremity Manual Muscle Test)				
Baseline	3.92 (0.070)	4.01 (0.042)	4.01 (0.054)	3.95 (0.053)
Average change	0.05 (0.024)	0.13 (0.014)	0.05 (0.024)	0.10 (0.024)
Difference	0.08		0.05	
p-value	0.003		0.106	
Ashworth Score (A test for muscle spasticity)				
Baseline	0.98 (0.078)	0.95 (0.047)	0.79 (0.058)	0.87 (0.057)
Average change	-0.09 (0.037)	-0.18 (0.022)	-0.07 (0.033)	-0.17 (0.032)
Difference	0.10		0.10	
p-value	0.021		0.015	

BID = twice a day

Study 218MS305

Study 218MS305 was conducted in 636 subjects with multiple sclerosis and walking disability. Duration of double-blind treatment was 24 weeks with a 2 week post–treatment follow-up. The primary endpoint was improvement in walking ability, measured as the proportion of patients achieving a mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks. In this study there was a statistically significant treatment difference, with a greater proportion of fampridine

treated patients demonstrating an improvement in walking ability, compared to placebo-controlled patients (relative risk of 1.38 (95% CI: [1.06, 1.70]). Improvements generally appeared within 2 to 4 weeks of initiation of treatment, and disappeared within 2 weeks of treatment cessation.

Fampridine treated patients also demonstrated a statistically significant improvement in the Timed Up and Go (TUG) test, a measure of static and dynamic balance and physical mobility. In this secondary endpoint, a greater proportion of fampridine treated patients achieved ≥ 15% mean improvement from baseline TUG speed over a 24 week period, compared to placebo. The difference in the Berg Balance Scale (BBS; a measure of static balance), was not statistically significant.

In addition, patients treated with fampridine demonstrated a statistically significant mean improvement from baseline compared to placebo in the Multiple Sclerosis Impact Scale (MSIS-29) physical score (LSM difference -3.31, p<0.001).

Table 3: Study 218MS305

Over 24 weeks	**Placebo N = 318***	**Fampridine 10 mg BID N = 315***	**Difference (95% CI) *P* - value**
Proportion of patients with mean improvement of ≥ 8 points from baseline MSWS-12 score	34%	43%	Risk difference: 10.4% (3% ; 17.8%) 0.006
MSWS-12 score			LSM: -4.14
Baseline	65.4	63.6	(-6.22 ; -2.06)
Improvement from baseline	-2.59	-6.73	< 0.001
TUG Proportion of patients with mean improvement of ≥ 15% in TUG speed	35%	43%	Risk difference: 9.2% (0.9% ; 17.5%) 0.03
TUG			LSM: -1.36
Baseline	27.1	24.9	(-2.85 ; 0.12)
Improvement from baseline (sec)	-1.94	-3.3	0.07
MSIS-29 physical score	55.3	52.4	LSM: -3.31
Baseline	-4.68	-8.00	(-5.13 ; -1.50)
Improvement from baseline			< 0.001
BBS score			LSM: 0.41
Baseline	40.2	40.6	(-0.13 ; 0.95)
Improvement from baseline	1.34	1.75	0.141

*Intent to treat population = 633; LSM = Least square mean, BID = twice a day

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing fampridine in all subsets of the paediatric population in treatment of multiple sclerosis with walking disability (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Fampridine has a narrow therapeutic index. Absolute bioavailability of fampridine prolonged-release tablets has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95%. The fampridine prolonged-release tablet has a delay in the absorption of fampridine manifested by slower rise to a lower peak concentration, without any effect on the extent of absorption.

When fampridine prolonged-release tablets are taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of fampridine is approximately 2-7% (10 mg dose). The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. However, C_{max} increases by 15-23%. Since there is a clear relationship between C_{max} and dose related adverse reactions, it is recommended to take fampridine without food (see section 4.2).

Distribution

Fampridine is a lipid-soluble active substance which readily crosses the blood-brain barrier. Fampridine is largely unbound to plasma proteins (bound fraction varied between 3-7% in human plasma). Fampridine has a volume of distribution of approximately 2.6 L/kg.
Fampridine is not a substrate for P-glycoprotein.

Biotransformation:

Fampridine is metabolised in humans by oxidation to 3-hydroxy-4-aminopyridine and further conjugated to the 3-hydroxy-4-aminopyridine sulfate. No pharmacological activity was found for the fampridine metabolites against selected potassium channels *in vitro*.

The 3-hydroxylation of fampridine to 3-hydroxy-4-aminopyridine by human liver microsomes appeared to be catalysed by Cytochrome P450 2E1 (CYP2E1).

There was evidence of direct inhibition of CYP2E1 by fampridine at 30 μM (approximately 12% inhibition) which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg tablet.

Treatment of cultured human hepatocytes with fampridine had little or no effect on induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities.

Elimination

The major route of elimination for fampridine is renal excretion, with approximately 90% of the dose recovered in urine as parent active substance within 24 hours. Renal clearance (CLR 370 mL/min) is substantially greater than glomerular filtration rate due to combined glomerular filtration and active excretion by the renal OCT2 transporter. Faecal excretion accounts for less than 1% of the administered dose.

Fampridine is characterized by linear (dose-proportional) pharmacokinetics with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase proportionately with dose. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with renal impairment, accumulation occurs relative to the degree of impairment.

Special populations

Elderly

Fampridine is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in elderly patients is recommended (see section 4.2).

Paediatric population:

No data are available.

Patients with renal impairment:

Fampridine is eliminated primarily by the kidneys as unchanged active substance and therefore renal function should be checked in patients where renal function might be compromised. Patients with mild renal impairment can be expected to have approximately 1.7 to 1.9 times the fampridine concentrations achieved by patients with normal renal function. Fampridine Accord must not be administered to patients with moderate and severe renal impairment (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Fampridine was studied in oral repeat dose toxicity studies in several animal species.

Adverse responses to orally administered fampridine were rapid in onset, most often occurring within the first 2 hours post-dose. Clinical signs evident after large single doses or repeated lower doses were similar in all species studied and included tremors, convulsions, ataxia, dyspnoea, dilated pupils, prostration, abnormal vocalization, increased respiration, and excess salivation. Gait abnormalities and hyper-excitability were also observed. These clinical signs were not unexpected and represent exaggerated pharmacology of fampridine. In addition, single cases of fatal urinary tract obstructions were observed in rats. The clinical relevance of these findings remains to be elucidated, but a causal relationship with fampridine treatment cannot be excluded.

In reproduction toxicity studies in rats and rabbits, decreased weight and viability of foetuses and offspring were observed at maternally toxic doses. However, no increased risk for malformations or adverse effects on fertility was noted.

In a battery of *in vitro* and *in vivo* studies fampridine did not show any potential to be mutagenic, clastogenic or carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose (E464)
Silica, colloidal anhydrous (E551)
Cellulose microcrystalline (E460)
Magnesium stearate (E572)

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-aluminium perforated unit-dose blister packs containing 28 x 1, 49 x 1, 56 x 1 tablets or multipacks containing 196 x 1 (4 packs of 49 × 1) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1477/001
EU/1/20/1477/002
EU/1/20/1477/003
EU/1/20/1477/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER (S) 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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Polska Sp.z.o.o.
Ul. Lutomierska 50,
95-200, Pabianice, Poland

Pharmadox Healthcare Ltd.
KW20A Kordin Industrial Park, Paola PLA3000, Malta

Laboratori Fundació DAU
C/ C, 12-14 Pol. Ind. Zona Franca, 08040 Barcelona, Spain

Accord Healthcare single member S.A.
64th Km National Road Athens, Lamia,
Schimatari, 32009,
Greece

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fampridine Accord 10 mg prolonged-release tablets
fampridine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of fampridine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet
28 x 1 prolonged-release tablet
56 x 1 prolonged-release tablet
49 x 1 prolonged release tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1477/001
EU/1/20/1477/002
EU/1/20/1477/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fampridine Accord

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Fampridine Accord 10 mg prolonged-release tablets
fampridine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of fampridine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet
196 × 1 (4 packs of 49 × 1) prolonged-release tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,

Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1477/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fampridine Accord

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Fampridine Accord 10 mg prolonged-release tablets
fampridine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of fampridine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablet
49 × 1 prolonged-release tablet. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,

Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1477/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fampridine Accord

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Fampridine Accord 10 mg prolonged-release tablets
fampridine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Leave 12 hours between each tablet

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fampridine Accord 10 mg prolonged-release tablets
fampridine

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 Fampridine Accord is and what it is used for

Fampridine Accord contains the active substance fampridine which belongs to a group of medicines called potassium channel blockers. They work by stopping potassium leaving the nerve cells which have been damaged by MS. This medicine is thought to work by letting signals pass down the nerve more normally, which allows you to walk better.

Fampridine Accord is a medicine used to improve walking in adults (18 years and over) with Multiple Sclerosis (MS) related walking disability. In multiple sclerosis, inflammation destroys the protective sheath around the nerves leading to muscle weakness, muscle stiffness and difficulty walking.

2. What you need to know before you take Fampridine Accord

Do not take Fampridine Accord

- if you are **allergic** to fampridine or any of the other ingredients of this medicine (listed in section 6)
- if you have a seizure or have ever had a **seizure** (also referred to as a fit or convulsion)
- if your doctor or nurse has told you that you have moderate or severe **kidney problems**
- if you are taking a medicine called cimetidine
- if you are **taking any other medicine containing fampridine**. This may increase your risk of serious side effects

Tell your doctor and **do not take** Fampridine Accord if any of these apply to you.

Warnings and precautions

Talk to your doctor or pharmacist before taking Fampridine Accord:
- if you feel aware of your heartbeat (*palpitations*)
- if you are prone to infections
- if you have any factors or are taking any medicine which affects your risk of fits (*seizure*).

- if you have been told by a doctor that you have mild problems with your kidneys.
- if you have history of allergic reactions

You should use a walking aid, such as a cane, as needed because this medicine may make you feel dizzy or unsteady this may result in an increased risk of falls.

Tell your doctor before you take Fampridine Accord if any of these apply to you.

Children and adolescents

Do not give this medicine to children or adolescents under the age of 18 years.

Elderly
Before starting treatment and during treatment your doctor may check that your kidneys are working properly.

Other medicines and Fampridine Accord

Tell your doctor or pharmacist if you are taking, have recently taken or might take **any other medicines**.

Do not take Fampridine Accord if you are taking any other medicine containing fampridine.

Other medicines that affect the kidneys

Your doctor will be especially careful if fampridine is given at the same time as any medicine which may affect how your kidneys eliminate medicines for example carvedilol, propranolol and metformin.

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 before for advice before taking this medicine.

Fampridine Accord is not recommended during pregnancy.

Your doctor will consider the benefit of you being treated with Fampridine Accord against the risk to your baby.

You should not breast-feed whilst taking this medicine.

Driving and using machines

Fampridine Accord may have an effect on people's ability to drive or use machines, it can cause dizziness. Make sure you are not affected before you start driving or use machinery.

3. How to take Fampridine Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Fampridine Accord is only available by prescription and under the supervision of doctors experienced in MS.

Your doctor will give you an initial prescription for 2 to 4 weeks. After 2 to 4 weeks the treatment will be reassessed.

The recommended dose is

One tablet in the morning and **one** tablet in the evening (12 hours apart). Do not take more than two tablets in a day. **You must leave 12 hours** between each tablet. Do not take the tablets more often than every 12 hours.

Fampridine Accord is for oral use.

Swallow each tablet whole, with a drink of water. Do not divide, crush, dissolve, suck or chew the tablet. This may increase your risk of side effects.

This medicine should be taken without food, on an empty stomach.

If you take more Fampridine Accord than you should

Contact your doctor immediately if you take too many tablets.
Take the Fampridine Accord box with you if you go to see the doctor.
In overdose you may notice sweating, minor shaking (*tremor*), dizziness, confusion, memory loss (*amnesia*) and fits (*seizure*). You may also notice other effects not listed here.

If you forget to take Fampridine Accord

If you forget to take a tablet, do not take two tablets at once to make up for a missed dose. You must **always leave 12 hours** between each tablet.

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.

If you have a seizure, stop taking Fampridine Accord and tell your doctor immediately.

If you experience one or more of the following allergic (*hypersensitivity***)** symptoms: swollen face, mouth, lips, throat or tongue, reddening or itching of the skin, chest tightness and breathing problems **stop taking Fampridine Accord** and see your doctor immediately.

Side effects are listed below by frequency:

Very common side effects

May affect more than 1 in 10 people:
- Urinary tract infection

Common side effects

May affect up to 1 in 10 people:
- Feeling unsteady
- Dizziness
- Spinning sensation (vertigo)

- Headache
- Feeling weak and tired
- Difficulty sleeping
- Anxiety
- Minor shaking (*tremor*)
- Numbness or tingling of skin
- Sore throat
- Common cold (*nasopharyngitis*)
- Flu (*influenza*)
- Viral infection
- Difficulty breathing (shortness of breath)
- Feeling sick (*nausea*)
- Being sick (*vomiting*)
- Constipation
- Upset stomach
- Back pain
- Heartbeat that you can feel (*palpitations*)

Uncommon side effects

May affect up to 1 in 100 people
- Fits (*seizure*)
- Allergic reaction (*hypersensitivity*)
- Severe allergy (*anaphylactic reaction*)
- Swelling of the face, lips, mouth or tongue (*angioedema*)
- New onset or worsening of nerve pain in the face (*trigeminal neuralgia*)
- Fast heart rate (*tachycardia*)
- Dizziness or loss of consciousness (*hypotension*)
- Rash/itchy rash (*urticaria*)
- Chest discomfort

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 Fampridine Accord

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 package after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via waste water 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 Fampridine Accord contains

- **The active substance** is fampridine.
    - Each prolonged-release tablet contains 10 mg of fampridine
- **The other ingredients** are:
- Tablet core: Hypromellose (E464), silica, colloidal anhydrous (E551), cellulose microcrystalline (E460), magnesium stearate (E572);
- Film coating: hypromellose (E464), titanium dioxide (E171), macrogol (E1521)

What Fampridine Accord looks like and contents of the pack

White to off white, oval shaped, biconvex, bevel-edged, film coated tablets, approximately 13.1 x 8.1 mm in dimensions, debossed with 'FH6' on one side and plain on other side.

Fampridine Accord 10 mg prolonged-release tablets are packed in perforated unit-dose blister packs containing 28 x1, 49 x 1, 56 x 1 tablets, or in multipacks of 196 x 1 tablets (comprising 4 cartons, each containing 49 × 1 tablets).

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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