ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 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.

An off-white, film coated, oval biconvex 13 x 8 mm tablet with flat edge debossed with A10 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fampyra 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 Fampyra 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). Fampyra 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).

Starting and Evaluating Fampyra 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 Fampyra
- 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, Fampyra should be discontinued
- Fampyra should be discontinued if benefit is not reported by patients.

Re-Evaluating Fampyra Treatment

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

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

Older people
Renal function should be checked in older people before starting treatment with Fampyra. Monitoring renal function to detect any renal impairment is recommended in older people (see section 4.4).

Patients with renal impairment
Fampyra is contraindicated in patients with mild, moderate and severe renal impairment (creatinine clearances <80 ml/min) (see section 4.3).

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

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

Method of Administration

Fampyra 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 mild, moderate or severe renal impairment (creatinine clearances <80 ml/min).

Concomitant use of Fampyra 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).

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

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

Renal impairment

Fampyra 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 older people in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.
Fampyra should not be administered to patients with renal impairment (creatinine clearance <80 ml/min) (see section 4.3).

Caution is required when Fampyra is prescribed concurrently with medicinal products that are substrates of OCT2 for example, carvedilol, propanolol 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, Fampyra should be discontinued and not restarted.

Other warnings and precautions

Fampyra 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 Fampyra 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 Fampyra 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, propanolol 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 Fampyra in pregnancy.

Breast-feeding

It is unknown whether fampridine is excreted in human or animal milk. Fampyra 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

Fampyra has a moderate influence on the ability to drive and use machines because Fampyra can cause dizziness.

4.8 Undesirable effects

The safety of Fampyra 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 Fampyra given at the recommended dose, are reported as urinary tract infection (in approximately 12% of patients).

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.

MedDRA 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 Paraesthesia Tremor Seizure Exacerbation of trigeminal neuralgia	Common Common Common Common Common Uncommon Uncommon
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular disorders	Hypotension[2]	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[2]	Common Uncommon

[1] See section 4.4

[2] These symptoms were observed in the context of hypersensitivity

Description of selected adverse reactions

Seizure

In post-marketing experience, there have been reports of seizure, the frequency is not known (cannot be estimated from the available data). For further information on seizure risk, please refer to sections 4.3 and 4.4.

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 Fampyra were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia.

Central nervous system side effects at high doses of 4-aminopyridine include 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

Fampyra is a potassium channel blocker. By blocking potassium channels, Fampyra 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 Fampyra dose was 10 mg 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 Fampyra 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 Fampyra 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 Fampyra.

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

Table 1: Studies MS-F203 and MS-F204

STUDY *	**MS-F203**		**MS-F204**	
	Placebo	**Fampyra 10 mg BID**	**Placebo**	**Fampyra 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	

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 Fampyra 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.

Fampyra 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 Fampyra 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 Fampyra 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 2: Study 218MS305

Over 24 weeks	**Placebo N = 318***	**Fampyra 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

The European Medicines Agency has waived the obligation to submit the results of studies with Fampyra 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 Fampyra prolonged-release tablets has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95%. The Fampyra 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 Fampyra 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 Fampyra without food (see section 4.2).

Distribution:

Fampridine is a lipid-soluble medicinal product 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 catalyzed 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 medicinal product 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.

Fampyra 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

Older people:

Clinical studies of Fampyra did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Fampyra is primarily excreted unchanged by the kidneys, and with creatinine clearance known to decrease with age, monitoring of renal function in older patients should be considered (see section 4.2).

Paediatric Population:

No data are available.

Patients with renal impairment:

Fampridine is eliminated primarily by the kidneys as unchanged medicinal product 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. Fampyra must not be administered to patients with mild, moderate and severe renal impairment (see section 4.3).

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
Microcrystalline cellulose
Silica, colloidal anhydrous
Magnesium stearate

Film-coat:

Hypromellose
Titanium dioxide (E-171)
Polyethylene glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening a bottle, use within 7 days.

6.4 Special precautions for storage

Store below 25°C. Store the tablets in the original packaging in order to protect from light and moisture.

6.5 Nature and contents of container

Fampyra is supplied in either bottles or blister packs.

Bottles
HDPE (high-density polyethylene) bottle with polypropylene caps, each bottle contains 14 tablets and a silica gel desiccant.
Pack size of 28 (2 bottles of 14) tablets.
Pack size of 56 (4 bottles of 14) tablets.

Blister packs
Foil blisters (aluminium / aluminium), each blister tray contains 14 tablets.
Pack size of 28 (2 blisters of 14) tablets.
Pack size of 56 (4 blisters of 14) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/699/001
EU/1/11/699/002
EU/1/11/699/003
EU/1/11/699/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2011
Date of latest renewal: 18 May 2017

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS(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 manufacturers responsible for batch release

Alkermes Pharma Ireland Ltd
Monksland
Athlone, Co. Westmeath
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 (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

BOTTLE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 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

28 prolonged-release tablets (2 bottles of 14 tablets each)
56 prolonged-release tablets (4 bottles of 14 tablets each)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For 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
After first opening a bottle, use within 7 days.

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Store the tablets in the original bottle 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

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/699/001 28 tablets
EU/1/11/699/002 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fampyra

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fampyra 10 mg prolonged-release tablets
fampridine
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP
After first opening a bottle, use within 7 days.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

14 prolonged-release tablets

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 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

28 prolonged-release tablets (2 blisters of 14 tablets each)
56 prolonged-release tablets (4 blisters of 14 tablets each)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For 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

Store below 25°C. Store the tablets in the original packaging 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

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/699/003 28 tablets
EU/1/11/699/004 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fampyra

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 10 mg prolonged-release tablets
fampridine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

leave 12 hours between each tablet

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: information for the user

Fampyra 10mg 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 Fampyra is and what it is used for
2. What you need to know before you take Fampyra
3. How to take Fampyra
4. Possible side effects
5. How to store Fampyra
6. Contents of the pack and other information

1. What Fampyra is and what it is used for

Fampyra 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.

Fampyra 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.

2. What you need to know before you take Fampyra

Do not take Fampyra

- 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 you have **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** Fampyra if any of these apply to you.

Warnings and precautions

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

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

Children and in adolescents

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

Older people

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

Other medicines and Fampyra

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

Do not take Fampyra 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, propanolol and metformin.

Fampyra with food and drink

Fampyra should be taken without food, on an empty stomach.

Pregnancy and breast-feeding

If you are pregnant, or are planning to become pregnant**, tell your doctor before** you take Fampyra

Fampyra is not recommended during pregnancy.

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

You should not breast-feed whilst taking this medicine.

Driving and using machines

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

3. How to take Fampyra

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Fampyra 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.

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.

If your Fampyra is supplied in bottles, the bottle will also contain a desiccant. Leave the desiccant in the bottle, do not swallow it.

If you take more Fampyra than you should

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

If you forget to take Fampyra

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 Fampyra 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 Fampyra** 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
- Headache
- Feeling weak and tired
- Difficulty sleeping
- Anxiety
- Minor shaking (*tremor*)
- Numbness or tingling of skin
- Sore throat
- Common cold (*nasopharyngitis*)
- Flu (*influenza*)
- 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*)
- Worsening of nerve pain in the face (*trigeminal neuralgia*)
- Fast heart rate (*tachycardia*)

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 Fampyra

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.

Store below 25°C. Store the tablets in the original packaging in order to protect from light and moisture.

If your Fampyra is supplied in bottles, only one bottle should be opened at a time. After first opening use within 7 days.

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

You can get a larger print version of this leaflet by calling the local representatives (see list below).

What Fampyra contains

- **The active substance** is fampridine.
- Each prolonged-release tablet contains 10 mg of fampridine
- **The other ingredients** are:
- Tablet core: hypromellose, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate; film coat: hypromellose, titanium dioxide (E-171), polyethylene glycol 400

What Fampyra looks like and contents of the pack

Fampyra is an off-white, film coated, oval biconvex 13 x 8 mm prolonged-release tablet with A10 on one side.

Fampyra is supplied in either blister packs or bottles.

Bottles

Fampyra comes in HDPE (high-density polyethylene) bottles. Each bottle contains 14 tablets and a silica gel desiccant. Each pack contains 28 tablets (2 bottles) or 56 tablets (4 bottles).

Blister packs

Fampyra comes in foil blisters of 14 tablets each. Each pack contains 28 tablets (2 blisters) or 56 tablets (4 blisters).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

Manufacturer:

Alkermes Pharma Ireland Ltd, Monksland, Athlone, Co. Westmeath, Ireland

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.