Physician Prescribing Information

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

1. NAME OF THE MEDICINAL PRODUCT

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 2 weeks of therapy as clinical benefits should generally be identified within 2-weeks after starting Fampyra
- A timed walking test, e.g. the Timed 25 Foot Walk (T25FW), is recommended to evaluate improvement after two 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 the walking test. Fampyra should be discontinued if patients no longer receive walking benefit.

Missed Dose
The usual dosing regime 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, 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 as stated below. An increased infection rate and impairment of the immune response cannot be excluded.

	Placebo-Controlled Studies 202/203/204		
System Organ Class Preferred Term	**Placebo (N=238)**	**Fampyra 10 mg BID (N=400)**	**TEAEs* with Incidence ≥1% in Fampyra vs**

			Placebo
Infections and Infestations (202/203/204)	**59 (24.8%)**	**124 (31.0%)**	**6.2%**
Gastroenteritis viral	4 (1.7%)	6 (1.5%)	-
Influenza	0 (0%)	6 (1.5%)	1.5%
Nasopharyngitis	4 (1.7%)	14 (3.5%)	1.8%
Pneumonia	1 (0.4%)	4 (1.0%)	-
Sinusitis	8 (3.4%)	6 (1.5%)	-
Upper respiratory tract infection	15 (6.3%)	20 (5.0%)	-
Urinary tract infection	20 (8.4%)	48 (12.0%)	3.6%
Viral infection	1 (0.4%)	6 (1.5%)	1.1%

* **TEAEs – Treatment Emergent Adverse Events**

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 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 no 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 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	Very 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
Vascular disorders	Hypotension*	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*	Common Uncommon

* 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

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

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

Two phase III, randomized, double-blind, placebo controlled confirmatory studies, (MS-F203 and MS-F204) have been performed. The majority of patients in these studies were using immunomodulatory medicines. The Fampyra dose was 10mg BID.

The primary endpoint 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 non-double blind off-treatment visits.

A significantly greater proportion of patients taking Fampyra 10 mg BID 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.

Pivotal 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) (Multiple Sclerosis Walking Scale)				
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, (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	

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).
The medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited, in particular about Fampyra's benefits beyond its effects on walking speed and with respect to early identification of responders. A study will be conducted to investigate this. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

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 (Cmax) 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 were 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
Colloidal silicon dioxide, 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 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 Idec Limited
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. LICENSE HOLDER

Medison Pharma Ltd, POB 7090, Petach Tikva.