SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fampyra 10 mg

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 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 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, the treatment should be discontinued

- This medicinal product 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 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

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

Fampyra is not indicated for children and adolescents under 18 years old

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

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).

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.
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, 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 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, 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. 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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 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 Tachycardia	Common 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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

Fampyra 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 Fampyra 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 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 the treatment.

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

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Table 2: 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)

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

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 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 3: 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 Improvement from baseline	65.4 -2.59	63.6 -6.73	(-6.22 ; -2.06) <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 Baseline Improvement from baseline (sec)	 27.1 -1.94	 24.9 -3.3	LSM: -1.36 (-2.85 ; 0.12) 0.07
MSIS-29 physical score Baseline Improvement from baseline	55.3 -4.68	52.4 -8.00	LSM: -3.31 (-5.13 ; -1.50) <0.001
BBS score Baseline Improvement from baseline	 40.2 1.34	 40.6 1.75	LSM: 0.41 (-0.13 ; 0.95) 0.141

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

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 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 Fampyra 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 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 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. Fampyra 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:

Hydroxypropyl methycellulose (Hypromellose)
Microcrystalline cellulose
Colloidal silicon dioxide, anhydrous

Magnesium stearate

Film-coat:

Hydroxypropyl methycellulose (Hypromellose)
Titanium dioxide
Macrogol (Polyethylene glycol 400)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

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.
After first opening a bottle, use within 7 days

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
aluminium / aluminium (oPA/Alu/HDPE/PE+CaO desiccant layer/Alu/PE) blisters, 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. MANUFACTURER

Merz Therapeutics GmbH
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8. LICENSE HOLDER

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