SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Fampridine Teva 10 mg, tabletten met verlengde afgifte

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, biconvex oval shaped film-coated prolonged-release tablets, debossed with R10 on one side. No debossing on the other side
Dimensions: approximately 8 x 13 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Product Name] 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 [Product Name] 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). [Product Name] 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 [Product Name] 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 [Product Name]
- 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, [Product Name] should be discontinued
- [Product Name] should be discontinued if benefit is not reported by patients.

Re-Evaluating [Product Name] 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 [Product Name] and performing an assessment of walking ability. [Product Name] 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.

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

Patients with renal impairment
Fampridine is contraindicated in patients with moderate and severe renal impairment (creatinine clearances <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 fampridine in children and adolescents aged 0 to 18 years have not been established. No data are available.

Method of administration

[Product Name] 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 the active substance 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 clearances <50 ml/min).

Concomitant use of fampridine 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).

Fampridine 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 elderly in whom renal function might be reduced). Creatinine clearance can be estimated using the Cockroft-Gault formula.

Caution is required when fampridine 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, [Product Name] 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 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 has a moderate influence on the ability to drive and use machines because fampridine can cause dizziness.

4.8 Undesirable effects

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).

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]	Very Common
	Influenza[1]	Common
	Nasopharyngitis[1]	Common
	Viral infection[1]	Common
Immune system disorders	Anaphylaxis	Uncommon
	Angioedema	Uncommon
	Hypersensitivity	Uncommon
Psychiatric disorders	Insomnia	Common
	Anxiety	Common
Nervous system disorders	Dizziness	Common
	Headache	Common
	Balance disorder	Common
	Vertigo	Common
	Paraesthesia	Common
	Tremor	Common
	Seizure[3]	Uncommon
	Exacerbation of trigeminal neuralgia	Uncommon
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular disorders	Hypotension[2]	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
	Pharyngolaryngeal pain	Common
Gastrointestinal disorders	Nausea	Common
	Vomiting	Common
	Constipation	Common
	Dyspepsia	Common
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Asthenia	Common
	Chest discomfort[2]	Uncommon

[1] See section 4.4
[2] These symptoms were observed in the context of hypersensitivity
[3] See sections 4.3 and 4.4

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 undesirable effects at high doses of 4-aminopyridine include dizziness, confusion, seizures, status epilepticus, involuntary and choreoathetoid movements. Other undesirable 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 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 fampridine.

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	**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	

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 2: 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	-1.94	-3.3	0.07
MSIS-29 physical score			LSM: -3.31
Baseline	55.3	52.4	(-5.13 ; -1.50)
Improvement from baseline	-4.68	-8.00	<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

Paediatric population

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 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 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.

Fampridine is characterised 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 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:
Calcium hydrogen phosphate dihydrate
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

AL/PVC/PVDC-aluminium blisters and unit-dose blisters.
OPA/AL/PE-aluminium blisters and unit-dose blisters with calcium oxide desiccant.

Pack sizes:
Blisters of 28 and 56 tablets and unit-dose blisters of 28x1 and 56x1 tablets.
Multipacks containing 196 (2 packs of 98) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Teva GmbH
Graf-Arco-Straße 3
89079 Ulm
Duitsland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 126649

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 24 november 2021

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 6.5: 1 maart 2023