NEW ZEALAND DATA SHEET

1. PRODUCT NAME

FAMPYRA® (fampridine) 10 mg Modified Release (MR) tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FAMPYRA 10 mg modified release tablet

Each tablet contains 10 mg fampridine.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

FAMPYRA 10 mg modified release tablet

Off white, oval bi-convex, film coated, modified release tablets with a flat edge, debossed with A10 on one side and plain on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FAMPYRA modified release tablets are indicated for the symptomatic improvement of walking ability in adult patients with Multiple Sclerosis who have shown improvement after 8 weeks of treatment.

4.2 Dose and method of administration

Dose

The recommended dosage of FAMPYRA for adults is one 10 mg tablet, twice daily, taken approximately 12 hours apart.

The usual dosing regime of one tablet in the morning and one tablet in the evening taken 12 hours apart should always be followed. A double dose should not be taken if a dose is missed.

As with all medicines, physicians should review the individual benefit/risk of FAMPYRA treatment with the individual patient to ensure continuing positive benefit/risk. Prescribers should re-evaluate the patient 8 weeks after the first treatment. Continued therapy should not be considered unless a walk test demonstrates response.

Paediatric population

Safety and effectiveness of FAMPYRA in patients younger than 18 years of age have not been established.

Elderly

Population pharmacokinetics showed that fampridine clearance modestly decreased with increased age, but not sufficiently to necessitate a dose adjustment with increasing age.

Renal impairment

FAMPYRA is eliminated through the kidneys primarily as unchanged drug and therefore, caution should be taken in prescribing FAMPYRA in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min or eGFR 60-89 mL/min/1.73m2). Renal function in these patients should be closely monitored as the clinical situation warrants.

Patients with moderate to severe renal impairment (Creatinine clearance <50 mL/min or eGFR less than 59 mL/min/1.73m2) should be excluded from treatment (see section 4.3).

Hepatic Impairment

FAMPYRA has not been studied in patients with hepatic impairment in clinical trials. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency is not expected to significantly affect fampridine pharmacokinetics. No dose adjustment is required for patients with hepatic impairment.

Method of administration

Tablets must be swallowed whole. As the tablets are modified release tablets, doses cannot be divided, crushed, dissolved, sucked or chewed. The tablets can be taken with or without food.

4.3 Contraindications

FAMPYRA is contraindicated in patients with known hypersensitivity to fampridine or any excipients in this product.

FAMPYRA should not be administered to patients with moderate or severe renal impairment (Creatinine clearance <50 mL/min or eGFR less than 59 mL/min/1.73m2).

FAMPYRA should not be administered to patients with prior history of seizure.

Prior to starting FAMPYRA all patients should be assessed for their risk of seizure by taking a full patient history. Patients who are considered by the physician to be at high risk of seizure should be excluded from treatment.

FAMPYRA should not be administered to patients currently on treatment with other forms of fampridine / 4-aminopyridine.

4.4 Special warnings and precautions for use

FAMPYRA should not be administered at doses higher than the recommended dose of 10 mg, twice daily, 12 hours apart.

Renal Impairment

Fampridine is primarily excreted unchanged through the kidneys. Patients with renal impairment may have higher plasma concentrations, which are associated with increased adverse drug reactions, in particular, neurological effects. Therefore, FAMPYRA should be used with caution, and monitoring of renal function considered in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min or eGFR 60-89 mL/min/1.73m2).

Particular caution is required when FAMPYRA is prescribed concurrently with drugs or medicinal products that can significantly impact renal function.

Seizures

A dose-dependent increase in risk of seizures has been observed in clinical studies with FAMPYRA at doses above the recommended 10mg taken twice daily. The recommended daily dose of FAMPYRA, 10mg, twice daily, taken 12 hours apart should not be exceeded.

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.

4.5 Interaction with other medicines and other forms of interaction

Fampridine is actively secreted unchanged by the kidneys; there is a theoretical possibility of an interaction with other drugs that are renally secreted (see section 5.2).

Organic Cation Transporter-2 (OCT2) is a renal transporter involved in the active secretion of fampridine). Cimetidine: In a single-dose clinical study, the OCT2 inhibitor cimetidine 400 mg every 6 hours and fampridine 10 mg single dose were concurrently administered to 23 healthy volunteers. The

test-reference ratio for AUC0–∞ was 125.1% (90% CI: 120.5%, 129.8%) due to a reduction in apparent clearance of FAMPYRA (CL/F). This increase in systemic exposure is not expected to be clinically meaningful.

In human liver microsomes in vitro, there was little evidence of a direct or metabolism- dependent inhibition of activities of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 by fampridine at concentrations up to 30μM (approximately 100 times the Cmax at the MRHD). Fampridine is therefore unlikely to inhibit CYP enzymes or affect the pharmacokinetics of drugs that are substrates of these enzymes, at therapeutic concentrations.

Treatment of cultured human hepatocytes with fampridine at concentrations up to 25μM (nearly 100 times the Cmax at the MRHD) for 3 days had little or no effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities. Thus, there is little potential for induction of these enzymes at therapeutic concentrations.

Fampridine is not a substrate or an inhibitor for the p-glycoprotein transporter in vitro. Thus, fampridine is unlikely to affect the pharmacokinetics of drugs that are substrates of p- glycoprotein and the pharmacokinetics of fampridine are unlikely to be affected by drugs that inhibit p-glycoprotein.

Interferon: Fampridine has been administered concomitantly with interferon-beta and no pharmacokinetic drug interactions were observed.

Baclofen: Fampridine has been administered concomitantly with baclofen and no pharmacokinetic drug interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Australian categorisation system for prescribing medicines in pregnancy: Category C

Adequate and well-controlled studies in pregnant women have not been conducted. FAMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive studies in rats and rabbits, when fampridine was administered orally at doses up to 10 mg/kg/day and 5 mg/kg/day, respectively, during the period of organogenesis, there was no evidence of embryotoxicity or teratogenicity, even at doses that were maternally toxic. In a study in which rats were dosed from early gestation to weaning, there were no effects on the offspring at a dose of 1mg/kg/day, giving a systemic exposure (plasma AUC) about 1.5- fold human exposure at the MRHD. Pup survival and weight gains were reduced at higher doses.

Breast-feeding

It is not known whether fampridine is excreted in human milk and the excretion of fampridine in milk has not been studied in animals. Lipophilic drugs pass easily into milk because of the high percentage of fat content in milk. Fampridine, being a lipophilic drug, may be excreted in human milk. Because of the potential for serious adverse reactions from fampridine in the breast-fed infant, a decision on whether to discontinue breast-feeding or to discontinue therapy with FAMPYRA should be made, taking into account the importance of FAMPYRA to the woman.

Fertility

No adverse effects on fertility were observed in rats following oral doses of fampridine up to 9 mg/kg/day in males and females treated prior to and during mating, continuing in females to late gestation or weaning. Exposure at this dose was equivalent to 8-fold the human exposure at the maximum recommended human dose (MRHD), based on plasma AUC, and maternal toxicity was observed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Central nervous system-related adverse reactions such as dizziness, vertigo and seizures associated with the use of FAMPYRA might influence the ability to drive and use machines, therefore caution should be

advised.

4.8 Undesirable effects

Clinical Trial Data

Summary of the safety profile

Adverse drug reactions are defined as those adverse events occurring at ≥1% higher frequency in the active treatment period with FAMPYRA than with placebo and considered with other fampridine data.

The highest incidence of adverse reactions identified from placebo-controlled trials in MS patients with FAMPYRA given at the recommended dose relate to nervous system excitation, as expected with the mechanism of action of FAMPYRA. These include insomnia, balance disorder, dizziness, headache and asthenia. Urinary Tract Infection (UTI) is also reported more frequently, although infection was often not proven. It is thought that this effect may be in part due to an effect of FAMPYRA to produce neuronal stimulation in the bladder mimicking symptoms of UTI.

Table 1: Adverse events occurring at ≥1% higher frequency in the active treatment period with FAMPYRA than with placebo

MedDRA SOC	Preferred Term	Frequency category
Infections and infestations	Urinary tract infection Nasopharyngitis	Very Common Common
Psychiatric disorders	Insomnia Anxiety	Common Common
Nervous system disorders	Balance disorder Dizziness Headache Paraesthesia Tremor	Common Common Common Common Common
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain Dyspnoea	Common Common
Gastrointestinal disorders	Nausea Vomiting Constipation Dyspepsia	Common Common Common Common
Musculoskeletal and connective tissue disorders	Back Pain	Common
General disorders and administration site conditions	Asthenia	Common

The safety profile of FAMPYRA 10 mg b.i.d. was also assessed in study 218MS305, a placebo-controlled study with 635 patients included in the safety population (placebo: N=319; FAMPYRA: N=316). The safety profile observed in this study was consistent with the known safety profile of FAMPYRA and no new safety concerns were identified.

Post marketing experience

Suspected adverse reactions reported in post-marketing experience that are not already included under “Clinical Trial Data” are described below. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Seizure

In post-marketing experience, there have been reports of seizure. Confounding factors may have contributed to the occurrence of seizure in some patients.

Hypersensitivity Reactions

Hypersensitivity reactions (including anaphylaxis) have been reported from post-marketing experience with fampridine.

Trigeminal Neuralgia

De novo symptoms or exacerbations of trigeminal neuralgia.

Vertigo

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Acute symptoms of overdose were consistent with central nervous system excitation and included dizziness, confusion, tremulousness, diaphoresis, seizure, and amnesia. The severity of symptoms is usually closely related to the pharmacokinetic exposure.

Treatment

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

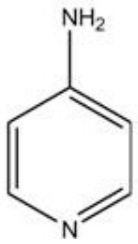
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Fampridine is also known by its chemical name, 4-aminopyridine with the following structure:



Fampridine is a fine white powder with a molecular weight of 94.1, CAS 504-24-5, a molecular formula of C5H6N2, an octanol/water partition coefficient (log P) of -0.76 and pKa of 9.17. At ambient conditions, fampridine is soluble in water (unbuffered ≥ 49 mg/mL, pH 7.0 buffered ≥ 57 mg/mL), methanol ≥ 53 mg/mL, acetone ≥ 52 mg/mL, tetrahydrofuran ≥ 52 mg/mL, isopropanol ≥ 52 mg/mL, acetonitrile ≥ 62 mg/mL, N, N-dimethylformamide ≥ 83 mg/mL, dimethylsulfoxide ≥ 78 mg/mL, and ethanol ≥ 77 mg/mL.

Mechanism of action

Fampridine is a non-selective potassium channel blocker and is a lipid-soluble drug which readily crosses the blood-brain barrier. Multiple Sclerosis (MS) is characterised by demyelination, and although the exact mechanism of action of fampridine is not known, fampridine is believed to act mainly by

blocking the potassium channels in demyelinated nerves, which reduces the leakage of current from the axons, restoring neuronal conduction and action potential formation.

FAMPYRA does not prolong the QTc interval and does not have a clinically important effect on QRS duration

Clinical efficacy and safety

The efficacy of FAMPYRA prolonged release tablets, (10 mg b.i.d) in improving walking ability in patients with ambulatory impairment, in all relapsing remitting and progressive forms of MS, was demonstrated in three phase III, randomised, double-blind, placebo controlled confirmatory studies, (MS-F203, MS-F204 and 218MS305). The proportion of patients displaying improvement in walking ability was independent of concomitant immunomodulatory therapy (including interferons, glatiramer acetate, fingolimod and natalizumab). No differences in effectiveness based on degree of impairment, age, gender or body mass index were detected.

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 quantitative test of walking ability that has been demonstrated to be a useful and reliable measure of the complex neurological process of walking. This responder rate analysis was performed to determine the number of patients who showed consistent improvement in walking speed during double-blind treatment, i.e., Timed Walk Responders. 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 open off-treatment visits.

The clinical meaningfulness of the primary endpoint (timed walk response) was validated by demonstrating significant association between improvements in walking speed with improvements on a patient self-assessment of walking disability, the 12- item Multiple Sclerosis Walking Scale (MSWS12).

The clinical meaningfulness of the improvement in T25FW in studies MS-F203 and MS-F204 was further validated by results from confirmatory study 218MS305. In this study, the primary endpoint was the proportion of patients demonstrating improvements on a patient self- assessment of walking disability, the 12-item Multiple Sclerosis Walking Scale (MSWS12). The MSWS12 questionnaire is a reliable and validated measurement of a patient's impression of the effect of their MS related walking disability over the previous two weeks on their ability to perform a range of activities of daily life, such as standing, climbing stairs, moving around the home and walking distances outside.

Studies MS-F203 and MS-F204

In studies MS-F203 and MS-F204 a significantly greater proportion of patients taking FAMPYRA 10 mg b.i.d had a consistent improvement in walking speed compared to patients taking placebo as measured by the T25FW, (MS-F203: 34.8% vs. 8.3%, $p<0.001$; MS-F204: 42.9% vs. 9.3%, $p<0.001$). The increased responder rate in the FAMPYRA cohort was observed across all types of MS disease included in the studies, independent of whether they were on DMT treatment or not. The Timed Walk Responders also demonstrated statistically significant mean improvement in walking speed (i.e., magnitude of timed walk response) compared to placebo (pooled results: 25.3% vs. 5.8%; $p<0.001$) as reported by % change from baseline T25FW score. The improvement appeared rapidly (within weeks) after starting treatment.

Changes from baseline MSWS-12 scores in studies MS-F203 and MS-F204, indicated that Timed Walk Responders taking FAMPYRA also demonstrated statistically and clinically significant, improvement in their ability to perform a range of activities of daily life, such as standing, climbing stairs, moving around the home and walking distances outside. Similarly, the SGI (Subject Global Impression) and CGI (Clinician Global Impression) scores showed responders had significantly greater improvement than non-responders. Pooled results from studies MS-F203 and MS-F204 also indicated a significant reduction in the Ashworth Score ($p<0.001$), which measures the degree of muscle spasticity, in the FAMPYRA cohort compared to placebo.

In study MS-F203, FAMPYRA also demonstrated significant improvements in leg strength compared to placebo, as measured by the Lower Extremity Manual Muscle Test (LEMMT), ($p<0.003$).

Study 218MS305

Study 218MS305 was a 24-week randomised, double-blind, placebo-controlled study. The Intent to Treat (ITT) population included 633 patients (315 on FAMPYRA) with Expanded Disability Status Scale (EDSS) scores ranging from 4 to 7. Patients included in the study were predominantly female (58%). The mean age was 49 years, the median disease duration was 10 years (mean 6.4 years) and the mean EDSS at screening was 5.48.

The primary endpoint in study 218MS305 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 (0.432 vs. 0.336; odds ratio: 1.61; p=0.006). 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 (0.434 vs. 0.347; odds ratio: 1.46; p=0.030).

The Multiple Sclerosis Impact Scale (MSIS-29), a patient reported outcome (PRO) measure to assess the change from baseline in a patient's physical well-being over 24 weeks, was an additional secondary endpoint in study 218MS305. In this measure, patients treated with FAMPYRA prolonged release tablets demonstrated a statistically significant mean improvement from baseline compared to placebo (Least Squares (LS) mean difference -3.31, p<0.001).

In addition, positive and sustained treatment effects were observed in the Berg Balance Scale (a measure of static balance) and ABILHAND questionnaire (a patient reported outcome measuring improvement in upper limb mobility), in both placebo and FAMPYRA treated patients although neither were statistically significant for FAMPYRA (p=0.141 and p=0.197, respectively).

Table 2: Primary and key secondary endpoints of study 218MS305

	Placebo N = 318	**FAMPYRA10 mg b.i.d. N = 315**	**Odds ratio (95% CI)**	***P* - value**
Proportion of patients with mean improvement of ≥ 8 points from baseline MSWS-12 score over 24 weeks	0.336	0.432	1.61 (1.15, 2.26)	0.006
Proportion of patients with mean improvement of≥ 15% in TUG speed over24 weeks	0.347	0.434	1.46 (1.04, 2.07)	0.030
LS mean change from baseline MSIS-29 physical score over 24 weeks **LS mean difference (95% CI)**	-4.68	-8.00 -3.31 (-5.13, -1.50)	N/A	<0.001

Observational Study 218MS401

Study 218MS401 was a Phase IV, multinational, observational study of FAMPYRA's safety and efficacy in routine medical practice. The study population included 4646 MS patients, predominantly female (65.75) with a median age of 52.6 years.

Analysis conducted using data from 589 MS patients ≥65 years old treated with FAMPYRA (representing 392.1 patient years) showed that the most commonly reported treatment emergent adverse events (TEAEs) among patients <65 years and patients ≥65 years were similar to the most commonly reported TEAEs for the overall safety population treated with (dal)fampridine.

Review of events in patients with a history of seizures, or at increased seizure risk due to other seizure lowering medication, or antiepileptic/anticonvulsant medications showed that the nature and types of safety events in these subpopulations were consistent with the overall safety population treated with (dal)fampridine. 32 patients (0.7%) had 33 seizure-related AEs (incident rate 0.9/100 patient years). The incidence of seizure in Study 218MS401 was similar to the incidence of seizure in previous studies with FAMPYRA and the background incidence of seizure among patients with MS.

A safety evaluation in patients with 12 months exposure to FAMPYRA (long-term safety) were consistent with the known safety profile of (dal)fampridine.

Overall, the safety profile observed in this study was consistent with the known safety profile of FAMPYRA and no new safety concerns were identified.

Post marketing analysis of efficacy data in Study 218MS401 showed that long-term treatment with FAMPYRA (for up to 12 months) consistently provided improvements in patient-reported physical and psychological scores as assessed by MSIS-29 and in physician-reported CGI-I assessment on walking ability.

5.2 Pharmacokinetic properties

Absorption

Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of FAMPYRA has not been assessed, but relative bioavailability (as compared to an aqueous oral solution) is 95%. FAMPYRA tablets have a prolonged release of fampridine characterised by a slower rise to and a lower peak concentration when compared to an immediate release formulation, without any effect on the extent of absorption.

When FAMPYRA is 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.

Distribution

Fampridine is largely unbound to plasma proteins (greater than 90%) and has a volume of distribution of 2.6 L/kg.

Biotransformation

Fampridine is metabolised by oxidation to 3-hydroxy-4-aminopyridine and further conjugated to the 3-hydroxy-4-aminopyridine sulfate. Negligible pharmacological activity was found for these fampridine metabolites against selected potassium channels in vitro.

The 3-hydroxylation of fampridine to 3-hydroxy-4-aminopyridine by human liver microsomes appeared to be catalysed by two or more kinetically distinct enzymes. CYP2E1 appeared to be the major enzyme responsible for the 3-hydroxylation of fampridine, based on correlation analysis, chemical inhibition studies and incubations with recombinant human CYP enzymes.

Elimination

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

Linearity

FAMPYRA is characterised by linear (dose-proportional) pharmacokinetics with a terminal elimination half-life of approximately 6 hours. The maximum plasma concentration (C_{max}) and area under the

plasma concentration-time curve (AUC) increase proportionately over a dose range of 5 to 40 mg. There is no evidence of clinically relevant accumulation of fampridine taken at the recommended dose in patients with full renal function. In patients with increasing amounts of renal impairment accumulation occurs in line with the degree of impairment.

5.3 Preclinical safety data

Genotoxicity

Fampridine was not genotoxic in in vitro assays (bacterial reverse mutation assay, mouse lymphoma tk assay, and chromosomal aberration test in Chinese Hamster Ovary cells), or in in vivo mouse and rat micronucleus tests.

Carcinogenicity

Fampridine did not cause any increase in tumours in lifetime dietary carcinogenicity studies in mice and rats. The highest dose used in mice was approximately 80 mg/kg/day, which produced an exposure (based on plasma AUC) that was 11-fold human exposure at the MRHD. The highest dose in rats was approximately 18 mg/kg/day, which produced an exposure (based on plasma AUC) that was 10-fold human exposure at the MRHD. There was a significant increase in uterine polyps in high dose female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose Microcrystalline cellulose Silicon dioxide Magnesium stearate

The film coat (Opadry White Y-1-7000) contains hypromellose, titanium dioxide and macrogol 400.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

3 years from date of manufacture stored at or below 25°C

6.4 Special precautions for storage

Do not store above 25°C. Store the tablets in the original bottle. Do not use after the expiry date printed on the pack. After first opening a bottle, use within 7 days

6.5 Nature and contents of container

Each pack contains 4 HDPE bottles with a polypropylene child-resistant closure. Each bottle contains 14 tablets and a silica gel desiccant (in total there are 56 tablets in each pack).

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

03 November 2011

10. DATE OF REVISION OF THE TEXT

20 May 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8 Sponsor	New sponsor name and address