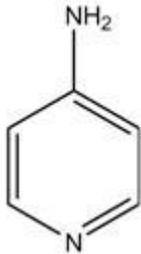


PRODUCT INFORMATION

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

NAME OF THE MEDICINE

FAMPYRA® (fampridine) is a 10 mg modified release white to off-white, film coated, oval shaped, biconvex, non-scored tablet with flat edge, debossed with "A10" on one side. 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 $C_5H_6N_2$, 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.

DESCRIPTION

FAMPYRA is a potassium channel blocker, available in a 10 mg tablet strength. Each tablet contains 10 mg fampridine, formulated as a modified release tablet for twice-daily oral administration. Each tablet also contains hypromellose, microcrystalline cellulose, silicon dioxide, magnesium stearate and the film coat (Opadry White Y-1-7000 E171) contains hypromellose, titanium dioxide and macrogol 400.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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 characterized 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.

Metabolism:

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 catalyzed 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.

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

CLINICAL TRIALS

Two phase III, randomised, double-blind, placebo controlled confirmatory studies, (MS-F203 and MS-F204) demonstrated the efficacy of FAMPYRA, (10mg b.i.d) in improving walking ability in patients with relapsing remitting, secondary progressive and primary progressive MS. The majority of patients in these trials were using immunomodulatory drugs, (including interferons, glatiramer acetate and natalizumab), however the magnitude of improvement in walking ability was independent of concomitant therapy.

No differences in effectiveness based on degree of impairment, age, gender or body mass index were detected.

The primary endpoint 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 non-double blind 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 MSWS12 questionnaire measures the 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.

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.

Based on change from baseline MSWS-12 scores, 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 FAMPYRA timed walk responders had significantly greater improvement than timed walk non-responders.

FAMPYRA also demonstrated significant improvements in leg strength, as measured by the Lower Extremity Manual Muscle Test (LEMMT), seen in the FAMPYRA 10mg b.i.d treatment group compared to placebo ($p < 0.003$) (MS-F203). Also, pooled results indicated a significant reduction in the Ashworth Score ($p < 0.001$), which measures the degree of muscle spasticity, in the FAMPYRA treatment compared to placebo group.

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.

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.

PRECAUTIONS

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.

Effects on 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.

Use 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.

Use in lactation

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.

Paediatric use

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

Use in the elderly

Clinical studies of FAMPYRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Population pharmacokinetics showed that fampridine clearance modestly decreased with increased age, but not sufficiently to necessitate a dose adjustment with increasing age.

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.

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.

Interactions with other medicines

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

Organic Cation Transporter-2 (OCT2) is a renal transporter involved in the active secretion of fampridine). The clinical consequence of the co-administration of fampridine with medicinal products that are substrates and/or inhibitors of OCT2 is unknown.

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 30 μ M (approximately 100 times the C_{max} 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 25 μ M (nearly 100 times the C_{max} 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.

Use in Renal or Hepatic 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, CONTRAINDICATIONS).

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.

Effects on Ability to Drive or Use Machines

No studies have been conducted.

ADVERSE EFFECTS

Clinical Trial Data

Adverse drug reactions are defined as those adverse events occurring at $\geq 1\%$ 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.

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

Post-Marketing Data

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.

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

Exacerbations of trigeminal neuralgia have been reported in patients with a history of trigeminal neuralgia.

DOSAGE AND ADMINISTRATION

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

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.

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.

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, CONTRAINDICATIONS).

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 reevaluate the patient 8 weeks after the first treatment. Continued therapy should not be considered unless a walk test demonstrates response.

OVERDOSAGE

Symptoms

Acute symptoms of overdose were consistent with central nervous system excitation and included 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

FAMPYRA (fampridine) 10 mg Modified Release Tablets are 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, each containing fampridine 10 mg.

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).

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.

NAME AND ADDRESS OF THE SPONSOR

Biogen Australia Pty Ltd
ABN 30 095 760 115
Level 3, 123 Epping Road
North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION ON THE ARTG

13 May 2011

DATE OF MOST RECENT AMENDMENT

13 Jan 2016

FAMPYRA[®] is marketed under license from Acorda Therapeutics, Inc. and is manufactured for Acorda under license from Alkermes Pharma Ireland Ltd. (APIL), utilizing APIL's Matrix Drug Absorption System (MXDAS[®]) technology. MXDAS[®] is a registered trademark of Alkermes Pharma Ireland Ltd. (APIL). FAMPYRA[®] is a registered trademark of Acorda Therapeutics, Inc.