PRODUCT MONOGRAPH

[Pr]pms-FAMPRIDINE
Fampridine Sustained Release Tablets

10 mg

Potassium Channel Blocker

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montréal, Québec
H4P 2T4

www.pharmascience.com

Date of Preparation:
February 10, 2020

Submission Control No: 217934

Table of Contents

[Pr]pms-FAMPRIDINE
Fampridine Sustained Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Sustained Release Tablet, 10 mg of fampridine per tablet	Colloidal Silicon Dioxide, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene glycol and Titanium Dioxide

INDICATIONS AND CLINICAL USE

pms-FAMPRIDINE (fampridine) sustained release tablets are indicated for the symptomatic improvement of walking in adult patients with multiple sclerosis (MS) with walking disability (EDSS 3.5-7). The initial prescription should be for no more than 4 weeks, and assessment for improvement in walking should be carried out within that timeframe (see DOSAGE AND ADMINISTRATION).

pms-FAMPRIDINE should only be prescribed by (or following consultation with) clinicians who are experienced in the management of multiple sclerosis and who are knowledgeable of the efficacy and safety profile of fampridine and are able to discuss the benefits/risks with patients.

Geriatrics (> 65 years of age)
Renal function should be checked in elderly patients before starting treatment with pms-FAMPRIDINE and monitored regularly. Use in patients with any degree of renal impairment (mild, moderate or severe) is contraindicated (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics (< 18 years of age)
Safety and efficacy of fampridine in patients younger than 18 years of age have not been evaluated. pms-FAMPRIDINE is not indicated for patients younger than 18 years of age.

CONTRAINDICATIONS

pms-FAMPRIDINE (fampridine) sustained release tablets are contraindicated:

- Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with fampridine. Therefore, pms-FAMPRIDINE is contraindicated in patients with a known hypersensitivity to the drug or to any ingredient in the formulation

or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING. See also WARNINGS AND PRECAUTIONS; and ADVERSE REACTIONS, Post Market Adverse Drug Reactions.

- In patients taking concurrent compounded 4-aminopyridine or other forms of fampridine.
- In patients with mild, moderate or severe renal impairment (creatinine clearance ≤ 80mL/min) (see WARNINGS AND PRECAUTIONS, Renal Impairment).
- In patients with a prior history or current presentation of seizure (see WARNINGS AND PRECAUTIONS, Seizure Risk).
- In patients taking medicinal products that are inhibitors of the renal Organic Cation Transporter 2 (OCT2), such as cimetidine and quinidine (see DRUG INTERACTIONS, ORGANIC CATION TRANSPORTER 2 (OCT2)).

WARNINGS AND PRECAUTIONS

SUMMARY OF IMPORTANT PRECAUTIONS TO BE TAKEN PRIOR TO INITIATING AND DURING TREATMENT WITH pms-FAMPRIDINE

- pms-FAMPRIDINE (fampridine) should be used under the supervision of a clinician experienced in the treatment of multiple sclerosis and familiar with the safety and efficacy of fampridine.
- Recommended dose should not be exceeded due to an increased risk of seizure (see DOSAGE AND ADMINISTRATION).
- Renal impairment and certain concomitant medications are among the factors that can result in increased fampridine plasma levels, and therefore result in increased risk of seizure (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, General).

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been observed in patients treated with fampridine. In several cases, these reactions occurred after the first dose. These hypersensitivity reactions included: anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, and urticaria. Patients should be informed of the signs and symptoms of a serious allergic reaction (e.g., itching, swelling of the face, tongue, throat, difficulty breathing, rash etc.). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms.

General

pms-FAMPRIDINE (fampridine) sustained release tablets should not be administered at doses higher than the recommended dose of 10 mg twice daily. One 10 mg tablet should be taken in the morning and one 10 mg tablet should be taken in the evening. The doses should be taken 12 hours apart. Treatment with fampridine increases seizure risk. A dose-dependent increase in risk of seizures has been observed in clinical studies with fampridine at doses above the recommended dose of 10 mg taken twice daily. In open label extension trials in MS patients, the incidence of seizures during treatment with fampridine 15 mg twice daily (1.7/100 patient years) was over 4 times higher than the incidence during treatment with 10 mg twice daily (0.4/100 patient years) (see WARNINGS AND PRECAUTIONS, Seizure Risk).

Renal Impairment

Fampridine is primarily excreted unchanged through the kidneys. Patients with renal impairment have higher plasma concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency), which are associated with increased adverse drug reactions, in particular neurological effects. Because patients with renal impairment would require a dose lower than 10 mg twice daily and dosage strengths less than 10 mg are not available, pms-FAMPRIDINE is contraindicated in patients with mild, moderate and severe renal impairment [Creatinine Clearance (CrCl) ≤ 80 mL/min] (see CONTRAINDICATIONS).

Determining renal function before treatment, and regular monitoring during treatment, is recommended in all patients. Creatinine clearance can be estimated using the Cockroft-Gault formula (multiply by 0.85 for women):

$$CrCl = \frac{(140 - age) \times weight(kg)}{SerumCr(mg/dl) \times 72}$$

Caution is required when pms-FAMPRIDINE is prescribed concurrently with drugs or medicinal products that can significantly impact renal function. These include substrates of OCT2, such as beta blockers (carvedilol, pindolol, propranolol), procainamide, metformin, ranitidine and varenicline. Inhibitors of OCT2 (including cimetidine and quinidine are contraindicated (see DRUG INTERACTIONS; CONTRAINDICATIONS).

Seizure Risk

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

Treatment in patients with a prior history or current presentation of seizure is contraindicated.

Prior to starting pms-FAMPRIDINE, 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 (see CONTRAINDICATIONS).

The risk of seizures is also increased with renal impairment, due to reduced clearance of fampridine (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency). Therefore, assessment of the risk of seizure should also include assessment of renal function prior to initiating treatment with pms-FAMPRIDINE. Treatment of patients with mild, moderate or severe renal impairment (creatinine clearance ≤ 80 mL/min) is contraindicated (see CONTRAINDICATIONS).

pms-FAMPRIDINE should be administered with caution in the presence of factors which may lower seizure threshold.

pms-FAMPRIDINE should be discontinued immediately in patients who experience a seizure while on treatment and not restarted.

Published epidemiological studies indicate that the MS population has a higher background prevalence of seizures than the general population (2 to 4% vs. 0.5 to 1%). This rate increases with age and progressive disease. In the MS population, the background incidence rate of first seizures has been reported to be in the range of 0.2 to 0.6 cases per 100 person-years. The seizure incidence observed during over 1,200 person-years of exposure in open-label treatment of MS patients with fampridine tablets 10 mg twice daily is consistent with this expected background rate (0.41 cases per 100 person-years).

In placebo controlled studies in MS, the incidence of seizure was not higher in the patients treated with fampridine 10 mg twice daily than in the placebo-treated patients (1/532 [0.19%] versus 1/249 [0.4%], respectively).

As seizures have been seen with the compounded form of fampridine and the immediate release formulations, the clinical trials were designed to exclude patients with a history of seizure or epileptiform activity. The safety data from the controlled trials has shown that at the recommended therapeutic dose (fampridine 10 mg twice daily), the risk of seizure is no higher than the placebo group.

Concurrent Treatment with Other Forms of 4-Aminopyridine

Concurrent treatment with other forms of 4-aminopyridine (4-AP, fampridine) is contraindicated since the active ingredient is the same (see CONTRAINDICATIONS). Patients should discontinue use of any product containing 4-aminopyridine prior to initiating treatment with pms-FAMPRIDINE in order to reduce the potential for dose-related adverse reactions.

Carcinogenesis and Mutagenesis

See Part II, Toxicology

Cardiovascular

Cardiac Conduction Disorders

pms-FAMPRIDINE is a potassium channel blocker and, therefore, 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 patients with cardiovascular disease as they were excluded from the clinical trials.

Immune

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 as stated below (Table 1). An increased infection rate and impairment of the immune response cannot be excluded.

Table 1: Infections and Infestations

	Placebo Controlled Studies 202/203/204		
	Placebo (n=238)	Fampridine10 mg BID (n=400)	TEAEs[a] with Incidence ≥1% in Fampridine vs Placebo
Infections and Infestations (202/203/204)	**59 (24.8%)**	**124 (31.0%)**	**6.2%**
Gastroenteritis viral	4 (1.7%)	6 (1.5%)	-
Influenza	0 (0%)	6 (1.5%)	1.5%
Nasopharyngitis	4 (1.7%)	14 (3.5%)	1.8%
Pneumonia	1 (0.4%)	4 (1.0%)	-
Sinusitis	8 (3.4%)	6 (1.5%)	-
Upper respiratory tract infection	15 (6.3%)	20 (5.0%)	-
Urinary tract infection	20 (8.4%)	48 (12.0%)	3.6%
Viral infection	1 (0.4%)	6 (1.5%)	1.1%

a TEAEs - Treatment Emergent Adverse Events

Neurological

Dizziness and Balance Disorder

The increased incidence of dizziness and balance disorder seen with fampridine may result in an increased risk of falls. Patients who are using walking aids should continue to use these aids as needed.

Exacerbation of Trigeminal Neuralgia

Exacerbation of Trigeminal neuralgia has been reported in MS patients with history of trigeminal neuralgia treated with fampridine during postmarketing experience (see ADVERSE REACTIONS, Post market Adverse Drug Reactions). In the majority of cases, onset was within 1 month of initiating treatment with fampridine and symptoms improved or resolved following discontinuation of fampridine, with or without pharmacological treatment of the trigeminal neuralgia. Some patients that received pharmacological treatment for adverse events of worsening trigeminal neuralgia required higher doses of previously effective treatments to manage symptoms.

Occupational Hazards

Since dizziness or fatigue may occur with the use of this drug, sensitive patients should be cautioned against activities requiring mental alertness and physical coordination until their response to the drug has been well-established.

Genitourinary

A higher incidence of urinary tract infections (UTI) was reported with fampridine (12%) than with placebo (8%), during controlled clinical trials. The underlying mechanism is not fully understood but may involve the effect of fampridine on the sensory and or motor innervation of the bladder. Adverse events of UTI were frequently reported based on symptoms of UTI without confirmation from urinalysis or culture results. Reported UTIs are usually moderate and transient.

Patient Counselling Information

Patients should be informed of the following:

- pms-FAMPRIDINE should be taken exactly as prescribed, one 10 mg tablet in the morning and one 10 mg tablet in the evening. Doses should be taken 12 hours apart.
- Do not take an extra dose after missing a dose.
- There is a dose-dependent risk of seizure. pms-FAMPRIDINE must be discontinued if they experience a seizure.
- Renal impairment increases plasma concentration of fampridine, which may lead to an increased risk of seizure. Advise patients that co-administration of certain drugs or medicinal products, such as beta blockers (carvedilol, pindolol, propranolol), procainamide, metformin, ranitidine and varenicline, can impact renal function.
- The assessment of improvement in walking should be done within 4 weeks of starting pms-FAMPRIDINE treatment. If there is no benefit to the patient seen within that time frame, treatment should be stopped.
- Patients should be informed of the signs and symptoms of a serious allergic reaction (e.g. itching, swelling of the face, tongue, throat, difficulty breathing, rash etc.). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies of fampridine in pregnant women. The use of pms-FAMPRIDINE during pregnancy should only be considered if the potential benefit to the mother justifies the potential risk to the fetus.

Administration of fampridine to animals during pregnancy resulted in decreased offspring viability and growth at doses 6.8 times the maximum recommended human dose (MRHD) of 20 mg/day (see TOXICOLOGY).

Nursing Women
It is not known whether fampridine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fampridine, pms-FAMPRIDINE is not recommended during breast feeding.

Pediatrics (<18 years of age)
The safety and efficacy of fampridine in patients younger than 18 years of age have not been evaluated. pms-FAMPRIDINE is not indicated for patients younger than 18 years of age.

Geriatrics (>65 years of age)
Clinical studies of fampridine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects (see ACTION AND CLINICAL PHARMACOLOGY). Because elderly patients are more likely to have decreased renal function, renal function should be determined in elderly patients before starting treatment with pms-FAMPRIDINE and monitored regularly.

Monitoring and Laboratory Tests
Clearance of fampridine is decreased in patients with renal impairment and is significantly correlated with creatinine clearance. Therefore, determining renal function before treatment and its regular monitoring during treatment is recommended in all patients who may be at risk of reduced renal function (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal Impairment, Special Populations; and ACTION AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Pre-market clinical trials in multiple sclerosis included 1,075 patients treated with fampridine for at least 12 weeks, 819 patients for 6 months, 628 patients for at least one year and 526 patients for at least two years.

Adverse reactions identified are mostly neurological and relate to nervous system excitation, including 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, and 8% in patients given placebo).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction

information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 lists treatment emergent adverse events that occurred during active treatment in ≥ 1% of fampridine-treated MS patients and more frequent compared to placebo in controlled clinical trials.

Table 2: Treatment-Emergent Adverse Events with an incidence of ≥ 1% of fampridine treated MS patients and at ≥ 1% higher rate than for placebo

Adverse Event	Placebo N=238	Fampridine 10 mg twice daily N= 400
Urinary tract infection	20 (8.4%)	48 (12.0%)
Insomnia	9 (3.8%)	35 (8.8%)
Dizziness	10 (4.2%)	29 (7.3%)
Headache	9 (3.8%)	28 (7.0%)
Nausea	6 (2.5%)	28 (7.0%)
Aesthenia	9 (3.8%)	27 (6.8%)
Back Pain	5 (2.1%)	20 (5.0%)
Balance Disorder	3 (1.3%)	19 (4.8%)
Paraesthesia	6 (2.5%)	16 (4.0%)
Nasopharyngitis	4 (1.7%)	14 (3.5%)
Constipation	5 (2.1%)	13 (3.3%)
Pharyngolaryngeal pain	2 (0.8%)	8 (2.0%)
Dyspepsia	2 (0.8%)	8 (2.0%)
Vomiting	1 (0.4%)	7 (1.8%)
Anxiety	1 (0.4%)	6 (1.5%)
Influenza	0 (0%)	6 (1.5%)
Viral infection	1 (0.4%)	6 (1.5%)
Pruritus	1 (0.4%)	6 (1.5%)
Tremor	0 (0%)	4 (1.0%)
Dyspnoea	0 (0%)	4 (1.0%)
White blood cell count decreased	0 (0%)	4 (1.0%)
Hypertriglyceridemia	0 (0%)	4 (1.0%)

Other Adverse Events Observed During Clinical Trials

The following is a list of treatment-emergent adverse events reported by patients treated with fampridine any dose and any formulation in the safety population (n=1,510). This population includes patients receiving fampridine during clinical pharmacology studies, placebo-controlled studies in patients with multiple sclerosis, placebo-controlled studies in patients with spinal cord injury and uncontrolled studies.

Events that have already been included in Table 2 have been excluded. Although the events reported occurred during treatment with fampridine, they were not necessarily caused by fampridine.

Events are listed by system organ class and frequency as defined as follows:

Frequent: occurring on 1 or more occasions in at least 1/100 patients
Infrequent: occurring in less than 1/100 but at least 1/1,000 patients
Rare: occurring in less than 1/1,000 patients.

Blood and lymphatic system disorders:
Infrequent: anaemia, lymph node pain
Rare: leukopenia, neutropenia

Cardiovascular:
Frequent: palpitations, tachycardia
Infrequent: atrioventricular block first degree, bundle branch block right, chest pain, coronary artery disease, ventricular extrasystoles, ventricular hypertrophy
Rare: bundle branch block left, dilatation ventricular

Ear and labyrinth disorders:
Frequent: tinnitus, vertigo
Infrequent: deafness bilateral, ear pain

Endocrine Disorders:
Infrequent: goitre
Rare: thyroid cyst

Eye Disorders:
Frequent: vision blurred, visual disturbance
Infrequent: blepharospasm, blindness, conjunctivitis, diplopia, eye haemorrhage, eye movement disorder, lacrimation increased, ocular hyperaemia, photopsia, scotoma
Rare: eyelid ptosis

Gastrointestinal disorders:
Frequent: abdominal discomfort, dry mouth, flatulence, stomach discomfort, toothache
Infrequent: abdominal hernia, abdominal pain lower, abdominal tenderness, dysphagia, epigastric discomfort, gastritis, haemorrhoidal haemorrhage, hypoaesthesia oral, irritable bowel syndrome
Rare: colitis, haematemesis

General disorders and administrative site conditions:
Frequent: chest discomfort, chest pain, chills, feeling hot, gait disturbance, influenza like illness, irritability
Infrequent: catheter related complication, cyst, gravitational oedema, injection site erythema, pitting oedema, suprapubic pain, tenderness

Immune System Disorders:
Frequent: hypersensitivity, seasonal allergy

Infections and Infestations:

Frequent: bronchitis, cystitis, ear infection, fungal infection, herpes simplex, tooth abscess, vulvovaginal mycotic infection

Infrequent: bacterial infection, candidiasis, escherichia urinary tract infection, eye infection, folliculitis, herpes virus infection, infection, labyrinthitis, laryngitis, localised infection, oral candidiasis, otitis externa, pharyngitis, pharyngitis streptococcal, rhinitis, sepsis, skin infection, subcutaneous abscess, tooth infection

Rare: abscess oral, bacterial pyelonephritis, clostridial infection, gingival abscess, paronychia, vaginal infection

Injury Poisoning and procedural complications:

Frequent: back injury, joint sprain, muscle strain, procedural pain, skin laceration, thermal burn

Infrequent: arthropod bite, arthropod sting, corneal abrasion, epicondylitis, eschar, fibula fracture, hand fracture, joint injury, laceration, ligament injury, neck injury, patella fracture, skeletal injury, sunburn, tendon injury, tooth fracture, wrist fracture

Rare: fracture, ligament sprain

Investigations:

Frequent: blood cholesterol increased, blood creatine phosphokinase increased, blood triglycerides increased, body temperature increased, white blood cell count increased

Infrequent: aspartate aminotransferase increased, blood creatinine increased, blood lactate dehydrogenase increased, blood phosphorus increased, blood potassium decreased, blood potassium increased, blood urea increased, cardiac murmur, carotid bruit, crystal urine present, electrocardiogram T wave inversion, electrocardiogram abnormal, full blood count abnormal, heart rate decreased, heart rate increased, heart rate irregular, hepatic enzyme increased, lymphocyte count decreased, monocyte count decreased, neutrophil count decreased, platelet count decreased, red blood cell count decreased, red blood cell count increased, red blood cells urine, red blood cells urine positive, weight increased, white blood cells urine

Rare: blood cholesterol abnormal, right ventricular systolic pressure increased, thyroxine increased, urine cytology abnormal

Metabolic and nutritional disorders:

Frequent: decreased appetite, hypercholesterolaemia

Infrequent: diabetes mellitus, hypokalaemia

Rare: polydipsia

Musculoskeletal and connective tissue disorders:

Frequent: bursitis, chest wall pain, muscle tightness, musculoskeletal discomfort, osteoporosis

Infrequent: bone pain, cervical spasm, groin pain, joint instability, limb discomfort, muscle twitching, musculoskeletal chest pain, osteoarthritis, osteopenia, pain in jaw, sensation of heaviness

Rare: trigger finger

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Infrequent: breast cancer, uterine leiomyoma

Rare: lentigo

Nervous system disorders:

Frequent: migraine, neuropathic pain, somnolence, trigeminal neuralgia

Infrequent: amnesia, dysaesthesia, dysgeusia, lethargy, Lhermitte's sign, motor dysfunction, myoclonus, neuralgia, nystagmus, peroneal nerve palsy, sciatica, sinus headache, syncope

Rare: anticholinergic syndrome, head titubation

Psychiatric disorders:

Frequent: abnormal dreams, confusional state, nervousness, sleep disorder

Infrequent: hallucination, panic attack, paranoia

*Renal and urinary disorders***:**

Frequent: dysuria, micturition urgency, urinary incontinence, urinary retention

Infrequent: bladder spasm, nephrolithiasis, nocturia, polyuria, pyuria, terminal dribbling, urinary hesitation

Reproductive system and breast disorders:

Infrequent: menorrhagia

Respiratory, thoracic and mediastinal disorders:

Frequent: nasal congestion, sinus congestion

Infrequent: asthma, atelectasis, epistaxis, hiccups, pharyngeal erythema, rhinorrhea, wheezing

Rare: nasal dryness, sinus disorder

Skin and subcutaneous tissue disorders:

Frequent: blister, ecchymosis, hyperhidrosis, skin ulcer

Infrequent: alopecia, cold sweat, dry skin, ingrown nail, livedo reticularis, purpura, rash macular, scab, skin lesion

Rare: drug eruption, hypotrichosis, skin fissures, telangiectasia

Vascular disorders:
Frequent: hot flush, hypertension, peripheral coldness
Infrequent: deep vein thrombosis, flushing, haematoma, hypotension, phlebitis
Rare: thrombosis

Seizures
Cases of seizure were reported infrequently during controlled clinical trials and open label extension studies with fampridine (5/532, 0.9 % and 5/660, 0.76%, respectively). Most of these incidences were associated with uncontrolled overdose, high systemic doses, or high plasma levels of fampridine (see WARNINGS AND PRECAUTIONS, Seizure Risk).

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during post marketing experience with fampridine: seizures, exacerbations of trigeminal neuralgia (TN) in patients with a history of TN (see WARNINGS AND PRECAUTIONS, Trigeminal Neuralgia) and hypersensitivity reactions (including anaphylactic/anaphylactoid reactions such as swollen tongue and swollen throat (pharyngeal edema) (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions). For the majority of cases of anaphylaxis, a relationship to fampridine could not be excluded.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Overview

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications.

Because fampridine is actively excreted unchanged by the kidneys; there is the potential for interactions with other drugs that are renally excreted (see PHARMACOKINETICS).

No pharmacokinetic drug interactions were observed between fampridine and interferon or baclofen. There was evidence of direct inhibition of CYP2E1 by fampridine at 30 mcM (approximately 12% inhibition) which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg tablet.

Interferon

No pharmacokinetic drug-drug interaction of interferon beta-1b was observed on fampridine plasma levels. Under single dose and steady-state conditions 7.5 mg t.i.d. of fampridine as an immediate release formulation was given alone and with subcutaneous injections of 8 million units interferon beta-1b. Immediate release fampridine was used to more closely approximate the

time to peak plasma levels for interferon. Fampridine kinetics were comparable following administration of fampridine alone (steady state C_{max} of 56.7 ng/mL and $AUC_{0-\infty}$ of 216.0 ng·hr/mL) or following co-administration of fampridine (steady state C_{max} of 50.1 ng/mL and $AUC_{0-\infty}$ of 207.2 ng·hr/mL) and Interferon beta 1-b in 3 male and 6 female MS patients.

Baclofen

No pharmacokinetic drug-drug interactions were observed on fampridine and baclofen plasma levels. Following a single oral dose of 15 mg fampridine (controlled release capsule formulation) administered to 12 healthy male volunteers, the mean C_{max} was 47.2 ng/mL and the mean $AUC_{0-\infty}$ was 399.8 ng·hr/mL and after a 10 mg dose of baclofen, the C_{max} was 199.5 ng/mL and the $AUC_{0-\infty}$ was 1 055.0 ng·hr/mL. When the same doses of fampridine and baclofen were co-administered, a similar C_{max} and $AUC_{0-\infty}$ were found: the fampridine C_{max} was 46.2 ng/mL and the $AUC_{0-\infty}$ was 402.5 ng·hr/mL and the baclofen C_{max} was 201.0 ng/mL and the $AUC_{0-\infty}$ was 1 024.4 ng·hr/mL.

CYP Enzymes

In vitro data with human liver microsomes showed that fampridine was not a direct or time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 at concentrations up to 30 mcM. There was evidence of direct inhibition of CYP2E1 by fampridine at 30 mcM (approximately 12 % inhibition), which is approximately 100 times the average plasma fampridine concentration measured for the 10 mg fampridine tablet.

Potential for Fampridine to Affect Other Drugs

The potential for 4-aminopyridine to induce human hepatocytes at therapeutic concentrations is remote. Other *in vitro* studies with cultured human hepatocytes with 0.025 mcM, 0.25 mcM, 2.5 mcM and 25 mcM fampridine had little or no effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities.

P-glycoprotein Transporter

In vitro, fampridine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of fampridine are unlikely to be affected by drugs that inhibit the P–glycoprotein transporter, and fampridine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter.

Organic Cation Transporter 2 (OCT2)

Fampridine is eliminated mainly via the kidneys with active renal secretion accounting for about 60% of elimination. *In vitro* studies have shown that the Organic Cation Transporter (OCT2) is the main transporter responsible for the active secretion of fampridine. Therefore, the concomitant use of fampridine with medicinal products that are inhibitors of OCT2 for example, cimetidine and quinidine, is contraindicated and concomitant use of fampridine with medicinal

products that are substrates of OCT2 for example, beta blockers (carvedilol, pindolol, propranolol), procainamide, metformin, ranitidine and varenicline is cautioned (see CONTRAINDICATONS; and WARNINGS AND PRECAUTIONS, Renal Impairment).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of pms-FAMPRIDINE (fampridine) sustained release tablets is one 10 mg tablet twice daily. One 10 mg tablet should be taken in the morning and one 10 mg tablet should be taken in the evening. The doses should be taken 12 hours apart.

Administration

Tablets should only be taken by swallowing whole with a glass of water. Doses should be taken without food.

Patients should be advised to not divide, crush, dissolve, suck or chew the tablet because broken tablets can release too much of the drug at one time and increase the risk of seizure adverse events. Patients should also be advised not to take an extra dose if a dose is missed, due to the increased risk of seizure adverse events.

Starting pms-FAMPRIDINE Treatment: Initial assessment of benefit

- The initial prescription for pms-FAMPRIDINE should be for no more than 4 weeks of therapy as clinical benefits should generally be identified within 4 weeks after starting pms-FAMPRIDINE.
- The assessment for evaluation of improvement should be conducted prior to starting treatment and again within 4 weeks.
- pms-FAMPRIDINE should be discontinued if benefit is not reported by patient.

Ongoing confirmation of positive benefit/risk profile

- Physicians should continue to actively review the benefit/risk of pms-FAMPRIDINE for the individual patient, to ensure continued positive benefit/risk.

In all cases, pms-FAMPRIDINE should be discontinued if patients no longer report benefit, or if seizure occurs.

Missed Dose

The dosing regimen of one tablet in the morning and one tablet in the evening taken 12 hours apart should always be followed. **Patients should be advised to not take an extra dose if a dose is missed.**

No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse events and discontinuations were more frequent at higher doses. In particular, the risk of seizure may increase with doses greater than 10 mg twice daily.

Dosing in Special Populations

Elderly
Renal function should be determined in elderly patients before starting treatment with pms-FAMPRIDINE. Monitoring renal function to detect any renal impairment is recommended in elderly patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Renal impairment
pms-FAMPRIDINE is contraindicated in patients with mild, moderate or severe renal impairment (Creatinine Clearance ≤ 80 mL/min) (see CONTRAINDICATIONS).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment.

Pediatric population
The safety and efficacy of fampridine in patients younger than 18 years have not been evaluated.

OVERDOSAGE

Acute symptoms of overdose with fampridine were consistent with central nervous system excitation and included confusion, tremulousness, diaphoresis, seizure, and amnesia. Central nervous system side effects at high doses of 4-aminopyridine include confusion, seizures, status epilepticus, involuntary and choreoathetoid movements. Other side effects at high doses include cases of cardiac arrhythmias (for example, supraventricular tachycardia and bradycardia) and ventricular tachycardia as a consequence of potential QT prolongation. Reports of hypertension have also been received.

Several cases of overdose are found in the scientific literature in which various formulations of fampridine were used, resulting in adverse events including seizure, confusion, tremulousness, diaphoresis and amnesia. In some instances, patients developed status epilepticus, requiring intensive supportive care and were responsive to standard therapy for seizures.

Three cases of overdose were reported in controlled clinical trials with fampridine sustained release tablets, involving two MS patients. The first patient took six times the currently recommended dose (60 mg) and was taken to the emergency room with altered mental state. The second patient took 40 mg doses on two separate occasions. In the first instance, the patient experienced a complex partial seizure, and, in the second instance, a period of confusion was reported. Both patients recovered by the following day without sequelae.

Patients with repeated seizure activity should be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which fampridine exerts its therapeutic effect has not been fully elucidated. Fampridine is a broad spectrum potassium channel blocker. In animal tissue preparations, fampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels.

Pharmacodynamics

Based on studies in animals, by blocking potassium channels, fampridine is thought to reduce the leakage of ionic current through these channels and enhance action potential formation in demyelinated axons. It is thought that by enhancing action potential formation, more impulses might be conducted in the central nervous system.

Pharmacokinetics

Absorption
Orally administered fampridine is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of sustained-release fampridine tablets has not been assessed, but relative bioavailability is 96% when compared to an aqueous oral solution. The sustained release tablet delays absorption of fampridine relative to the solution formulation manifested by slower rise to a lower peak concentration (C_{max}), with no effect on the extent of absorption (AUC).

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.

Distribution
Fampridine is largely unbound to plasma proteins (97–99%). The apparent volume of distribution is 2.6 L/kg.

Metabolism
Fampridine is metabolized 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*.

In vitro studies with human liver microsomes indicate that CYP2E1 was the major enzyme responsible for the 3-hydroxylation of fampridine based on correlation analysis, chemical

inhibition studies and incubations with recombinant human CYP enzymes. The identity of the CYP enzymes suspected of playing a minor role in the 3-hydroxylation of fampridine could not be established unequivocally.

Excretion
Fampridine and metabolites are eliminated nearly complete after 24 hours with 95.85% of the dose recovered in the urine and 0.51% recovery in feces. Most of the excreted radioactivity in the 0–4 hour pooled urine was parent drug (90.3%). Two metabolites were identified: 3- hydroxy-4-aminopyridine (4.3%) and 3-hydroxy-4-aminopyridine sulfate (2.6%).

The elimination half-life of fampridine following administration of the sustained-release tablet formulation of fampridine is 5.2 to 6.5 hours. The plasma half-life of the sulfate conjugate is approximately 7.6 hours and the half-life of 3-hydroxy-4-aminopyridine could not be calculated because concentrations for most subjects were close to or below the limit of quantitation.

Special Populations and Conditions

Pediatrics
The pharmacokinetics of fampridine in the pediatric population has not been studied. pms-FAMPRIDINE is not indicated for patients younger than 18 years of age.

Geriatrics
Clinical studies of fampridine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Because fampridine is primarily excreted unchanged by the kidneys, and creatinine clearance decreases with age, monitoring of renal function in elderly patients is recommended (see WARNINGS AND PRECAUTIONS, Special Populations, and Renal Impairment).

Gender
A population pharmacokinetic analysis suggested that female patients would be expected to have higher maximum fampridine plasma concentration than male patients. The magnitude of these relationships is small and does not necessitate any dose modifications.

Renal Insufficiency
The pharmacokinetics of fampridine was studied in 9 male and 11 female subjects with varying degrees of renal function. Elimination of the drug is significantly correlated with the creatinine clearance. Total body clearance of fampridine was reduced in patients with impaired renal function by 42.7% in mild (CLcr $\geq$ 50–80 mL/min), 50.3% in moderate (CLcr = 30–50 mL/min), and 72.7% in severe (CLcr $\leq$ 30 mL/min). The terminal half-life of fampridine is prolonged by 3.3-fold in severe renal impairment but not prolonged in mild or moderate impairment.

Fampridine is contraindicated in patients with renal impairment (see CONTRAINDICATIONS).

Hepatic Impairment

The pharmacokinetics of fampridine have not been studied in subjects with hepatic impairment. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency is not expected to significantly affect fampridine pharmacokinetics or recommended dosing.

Race
There was an insufficient number of non-Caucasians to evaluate the effect of race.

STORAGE AND STABILITY

Store pms-FAMPRIDINE (fampridine) sustained release tablets between 15 to 30°C in the original container. Protect from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-FAMPRIDINE (fampridine) sustained release tablets are film-coated, white to off-white, biconvex, oval shaped, beveled edge tablets, debossed "D10" on one side and plain on other side.

pms-FAMPRIDINE (fampridine) sustained release tablets containing 10 mg fampridine. Non-medicinal ingredients: Colloidal Silicon Dioxide, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol and Titanium Dioxide.

pms-FAMPRIDINE (fampridine) sustained release tablets are available in:

Bottles: 60 tablets with a natural plastic canister containing silica gel granules.
Blisters: 10 tablets in Alu-Alu blister pack.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: fampridine

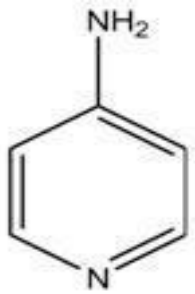
Chemical name: 4-aminopyridine

CAS: 504-24-5

Molecular formula: $C_5H_6N_2$

Molecular mass: 94.11 g/mol

Structural formula:



Physicochemical properties

Physical Form: white to off white crystalline powder

Solubility: At ambient temperature, fampridine is soluble in water, methanol, acetone, tetrahydrofuran, isopropanol, acetonitrile, *N*, *N*-dimethylformamide, dimethylsulfoxide and ethanol.

pH (1% solution): 11.16
pKa value: 9.17

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral comparative bioequivalence study of pms-FAMPRIDINE (Fampridine) Sustained Released Tablets 10 mg was performed versus [Pr]Fampyra™' (Fampridine) Sustained Release Tablets 10 mg in 26 healthy, adult, human subjects under fasting conditions Bioavailability data were measured and the results are summarized in the following table:

Fampridine (1 × 10 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/ mL)	332.73 338.64 (18.33)	324.56 332.67 (22.23)	102.5	98.0 -107.2
AUC_I (ng.hr/ mL)	349.30 356.93 (20.33)	341.38 351.56 (23.99)	102.3	94.7 - 107.5
C_{max} (ng/ mL)	28.37 28.61 (13.00)	28.82 29.19 (16.16)	98.4	94.4 - 102.6
T_{max}§ (h)	3.75 (2.00- 6.00)	3.25 (1.50 - 5.00)		
$T_{½}$€ (h)	4.85 (16.32)	4.93 (19.54)		

* pms-FAMPRIDINE (Fampridine) Sustained Release Tablets 10 mg (Pharmascience Inc.)
† [Pr]Fampyra™ (Fampridine) Sustained Release Tablets 10 mg, (Biogen Canada Inc.)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

A double blind, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral comparative bioequivalence study of pms-FAMPRIDINE (Fampridine) Sustained Released Tablets 10 mg was performed versus [Pr]Fampyra™' (Fampridine) Sustained Release Tablets 10 mg in 26 healthy, adult, human subjects under fed conditions Bioavailability data were measured and the results are summarized in the following table:

Fampridine (1 × 10 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/ mL)	296.51 299.10 (13.23)	294.52 297.01 (13.40)	100.7	98.0 - 102.7
AUC_I (ng.hr/ mL)	306.06 308.79 (13.34)	303.92 306.64 (13.73)	100.7	98.5 - 102.9
C_{max} (ng/ mL)	30.31 30.56 (13.35)	29.33 29.61 (13.99)	103.3	101.1 - 105.6
T_{max}§ (h)	4.25 (2.00- 6.00)	3.75 (2.50 - 6.00)		
$T_{½}$€ (h)	4.35 (13.60)	4.33 (13.09)		

* pms- FAMPRIDINE (Fampridine) Sustained Release Tablets 10 mg (Pharmascience Inc.)
† PrFampyra™ (Fampridine) Sustained Release Tablets 10 mg, (Biogen Canada Inc.)
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

The efficacy of fampridine sustained release tablets in improving walking in patients with multiple sclerosis was evaluated in two adequate and well controlled trials involving 540 patients (MS-F203 and MS-F204). Patients in these two clinical trials had a mean disease duration of 13 years and a median Kurtzke Expanded Disability Status Scale (EDSS) score of 6. Patient inclusion criteria included the ability to walk 25 feet in 8 to 45 seconds. Patient exclusion criteria included a history of seizures or evidence of epileptiform activity on a screening EEG, and onset of an MS exacerbation within 60 days.

MS-F203 was a randomized, placebo-controlled, parallel group, 21-week study (one week post screening, two-week, single-blind placebo run-in, 14-week double-blind treatment, and 4-week no treatment follow-up) in 301 patients with multiple sclerosis at 33 centers in the U.S. and Canada: 229 patients assigned to fampridine 10 mg b.i.d. and 72 patients assigned to placebo. A total of 283 patients (212 fampridine and 71 placebo) completed all study visits.

MS-F204 was a randomized, placebo-controlled, parallel group, 14-week study (one week post-screening, two weeks of single-blind, placebo run-in, nine weeks of double-blind treatment, and two weeks of no-treatment follow-up) in 239 patients with multiple sclerosis at 39 centers in the U.S. and Canada: 120 patients assigned to 10 mg twice daily and 119 assigned to placebo. A total of 227 patients (113 fampridine and 114 placebo) completed all study visits.

The primary measure of efficacy in both trials was walking speed (in feet per second) as measured by the Timed 25-foot Walk (T25W), using a responder analysis. A responder was defined as a patient who showed faster walking speed for a least three visits out of a possible

four during the double-blind period than the maximum value achieved in the five non-double-blind no treatment visits (four before the double-blind period and one after).

Study results

A significantly greater proportion of patients taking fampridine 10 mg twice daily were responders, compared to patients taking placebo, as measured by the T25FW (MS-F203: 34.8% vs. 8.3%; MS-F204: 42.9% vs. 9.3%). The increased response rate in the fampridine group was observed across all four major types of MS disease course.

During the double-blind treatment period, a significantly greater proportion of patients taking fampridine 10 mg twice daily had increases in walking speed of at least 10%, 20%, or 30% from baseline, compared to placebo (Figure 1 and Figure 2).

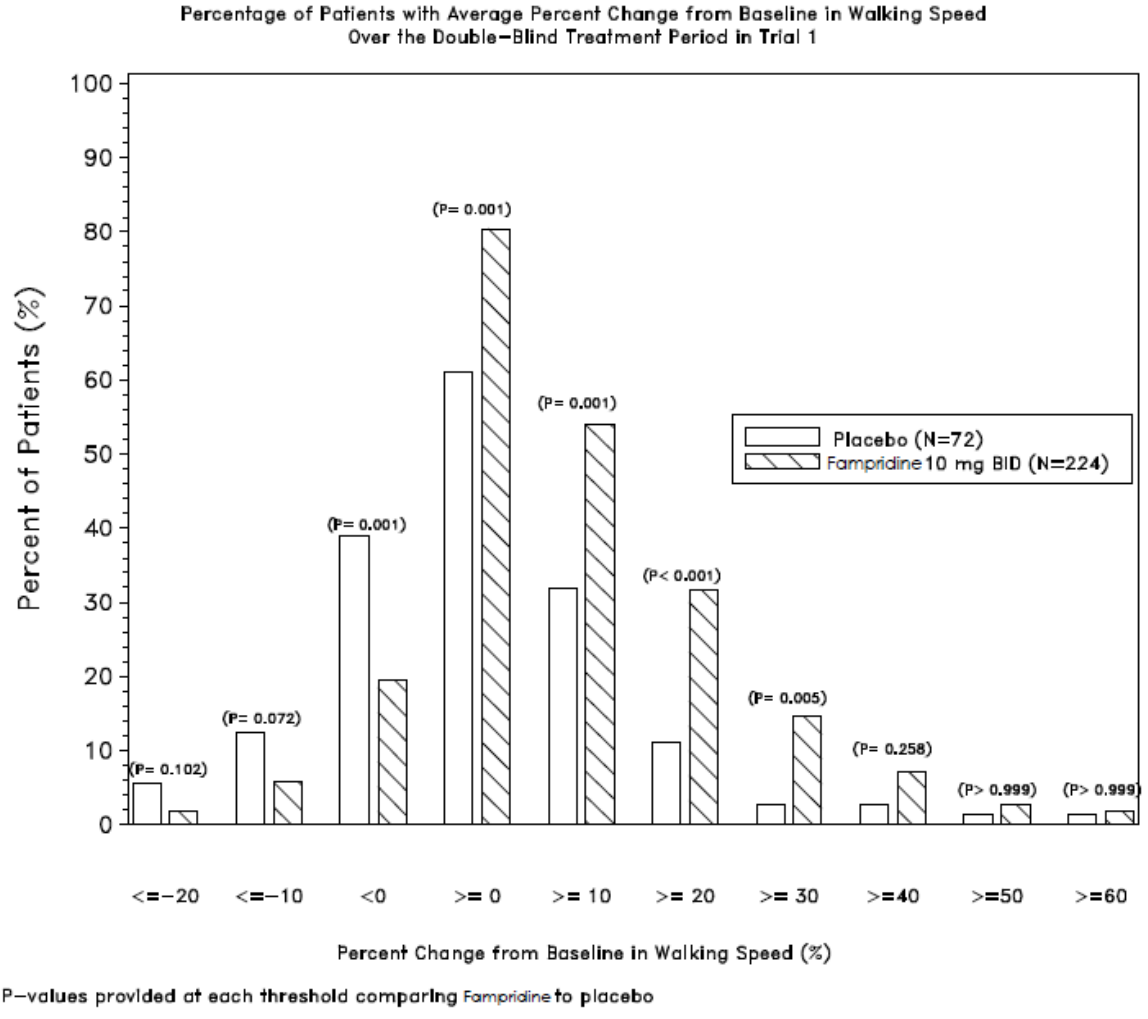
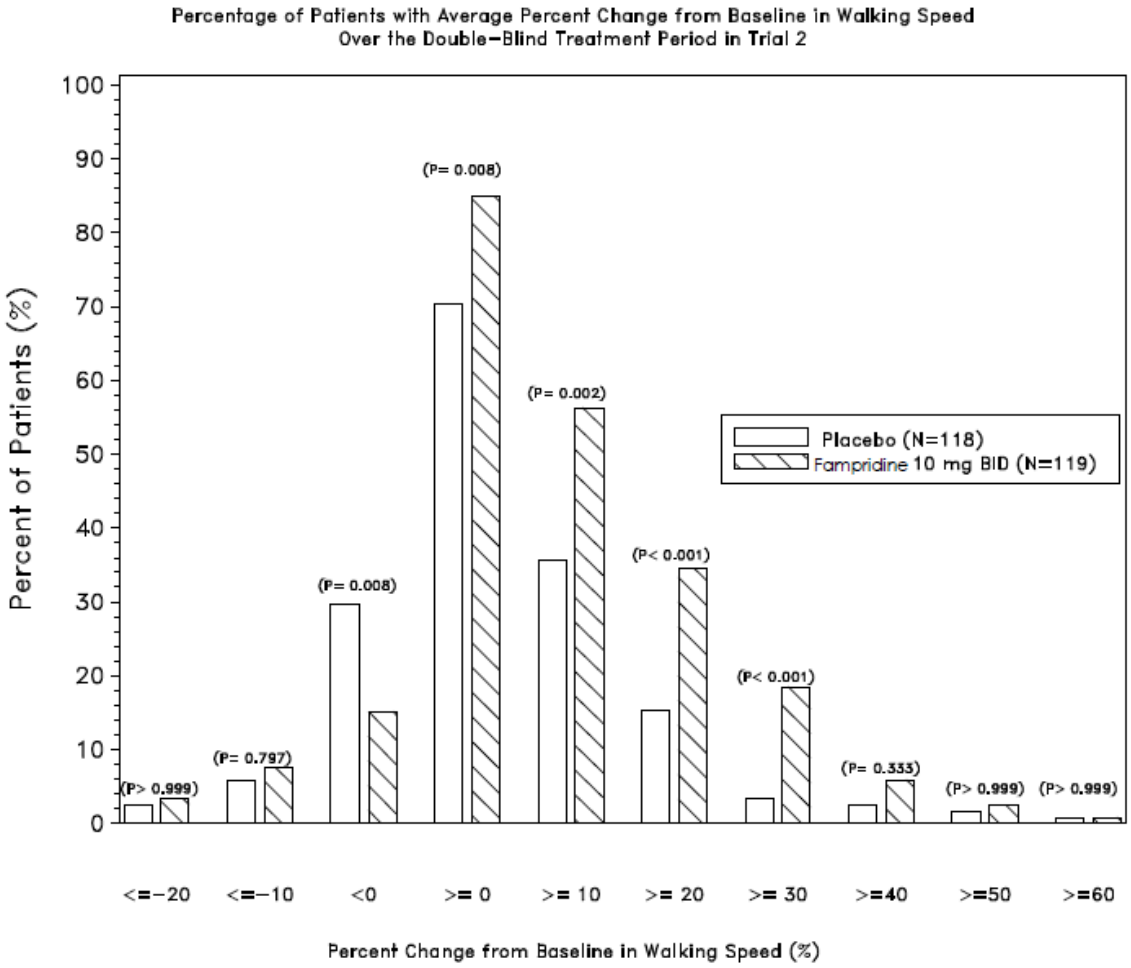


Figure 1: Average walking speed change (%) from baseline during the double-blind phase of MS-F203.

Figure 2: Average walking speed change (%) from baseline during the double-blind phase of MS-F204.



P-values provided at each threshold comparing fampridine to placebo"

Beneficial response to fampridine was found to be independent of MS disease course (relapsing or progressive, including primary progressive), independent of concomitant treatment with the major immunomodulatory drugs approved for this condition, and similar in magnitude across the full range of baseline ambulatory deficits examined, including patients with Expanded Disability Status Scores (EDSS) from 2.5 to 7. No differences in efficacy based on degree of impairment, age, gender, or body mass index were detected. There were too few non-Caucasians in the patient population to evaluate the effect of race.

In both studies, consistent improvements in walking speed were shown to be associated with improvements on a patient self-assessment of ambulatory disability, the 12-item Multiple Sclerosis Walking Scale (MSWS-12), for both drug and placebo treated patients.

DETAILED PHARMACOLOGY

Mechanism of Action

Fampridine (4-aminopyridine, 4-AP) blocks multiple potassium channels. When the axon is demyelinated the internodal membrane and its ion channels become exposed to larger electrical transients during the passage of an action potential. Leakage of ionic current through the potassium channel, under these conditions, then contributes to impairment of action potential conduction through the axon. In animal tissue preparations, 4-AP has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels. Fampridine is thought to reduce the leakage of ionic current through these channels and enhance action potential formation in demyelinated axons.

Safety Pharmacology

Fampridine was shown to inhibit hERG (human ether-à-go-go related gene) channel current *in vitro* but only at very high concentrations, e.g. hERG IC50 equals 3.83 mM (360,000 ng/mL), a value that is > 15,000 times the clinical C_{max} of ~0.23 mcM (~22 ng/mL).

In Purkinje fibers isolated from dogs *ex vivo*, 4-AP significantly ($P < 0.05$) prolonged action potential duration of all three repolarization levels (APD30, APD50, APD90) only at the highest concentration tested, 500 mcM (47 mcg/mL), which corresponds to > 2,000 times the clinical C_{max} of ~0.23 mcM (~22 ng/mL).

In dogs *in vivo*, at fampridine doses that resulted in peak systemic exposure of 13–21 mcM (1.25–2.0 mcg/mL), >50 times the clinical C_{max}, no changes in ECG parameters were observed.

Non-Clinical Pharmacokinetics

Pharmacokinetic (PK) parameters of 4-AP have been determined in rats, guinea pigs and dogs and toxicokinetic (TK) parameters of 4-AP have been determined in mice, rats, rabbits and dogs.

The primary routes of administration in rats and dogs were intravenous (i.v.) or oral (p.o.). In the guinea pig, the administration routes were i.v. and intramuscular (i.m.). When adjusted for differences in body surface area, the doses studied were similar to those used in humans. Of the nonclinical species tested, the ADME properties of 4-AP have been most comprehensively studied in rats. Overall, the absorption, distribution, metabolism and excretion of 4-AP are similar across all species examined including humans.

Following oral administration, 4-AP is rapidly absorbed with peak systemic exposure occurring within 1.5 hours. In rats, the absolute bioavailability is > 50% and, in humans, it is 95%. With repeated doses, 4-AP does not accumulate systemically. Systemic exposure to 4-AP increases with increasing dose; although the increase is less than dose proportional.

The volume of distribution of 4-AP in rats, guinea pigs, dogs and in humans is high, exceeding body water. 4-AP does not bind appreciably to plasma proteins (< 25% bound in rats, dogs and humans). In rats, 4-AP distributes into most tissues including the brain.

4-AP is partially metabolized, more extensively in rats and dogs than in humans. 4-AP is metabolized primarily by hydroxylation, followed by sulfate conjugation, and in rats, approximately one-third of the dose is cleared by hepatic first-pass metabolism. In humans, the predominant cytochrome P450 (CYP) isozyme responsible for 3-hydroxylation is CYP2E1. In rats and dogs, the primary metabolites identified through radiolabeled studies are 3-hydroxy-4-aminopyridine (3-OH-4-AP) and 3-OH-4-AP sulfate. These are also the predominant metabolites in mice, rabbits and humans. By 24 hours post radiolabeled drug administration, only 1% of the dosed radioactivity is still present in rats. In radiolabeled studies in rats and dogs, between 75 and 92% of the dose is excreted in urine within the first 12 hours, approximately 40% of which is the unchanged parent compound. In rats and dogs, *versus* humans, the clearance rate is higher (> 20 *versus* 9 mL/min/kg) and the elimination half-life ($t_{1/2}$) is shorter (1–2 *versus* ~4 hours). CYP inhibition studies in human microsomes demonstrated that 4-AP does not inhibit activity of the major metabolizing CYP isozymes. Studies with hepatocytes showed that 4-AP cultured human hepatocytes had little or no effect on CYP1A2, 2B6, 2C9, 2C19, 2E1 or 3A4/5 activity. The likelihood of 4-AP-mediated CYP dependent drug-drug interactions taking place through induction or inhibition of CYP activity in humans appears to be remote. 4-AP is renally excreted.

TOXICOLOGY

The preclinical safety of 4-AP was assessed in mice, rats, rabbits and dogs. The dosing regimen greatly affected the rate of mortality and incidence of adverse clinical signs in all species studied. In general, higher rates of mortality and adverse clinical signs were noted when 4-AP was administered in a single large dose as compared to administration by multiple (two, three, or four) equally divided sub-doses, or when administered through dietary admixture. This suggested that peak plasma levels may be more important than total exposure when considering toxicity of 4-AP.

Toxic responses to orally administered 4-AP were rapid in onset and included tremors, convulsions, ataxia, dyspnea, dilated pupils, prostration, abnormal vocalization, increased respiration, excess salivation, gait abnormalities, and hyper- and hypo-excitability. These clinical signs were not unexpected and represent exaggerated pharmacology of 4-AP. In single- dose studies in rats and in repeated-dose studies in dogs, gross necropsy findings observed in animals that died prematurely included discolorations of the kidney, lung and liver, thymus and spleen. In a 1 year repeated-dose study in dogs, these lesions were evaluated histologically, and were characterized as congestion and hemorrhage secondary to convulsion. In repeated-dose studies, no histological evidence of target organ toxicity was observed in either rats or dogs that survived to scheduled termination, aside from glandular dilation of the stomach in treated rats. Exposures associated with the no adverse effect levels (NOAEL) in these species were between 2- (rat, glandular dilation of the stomach) and 10-fold above those achieved in humans at the MRHD of 10 mg administered twice daily (b.i.d).

No evidence of carcinogenicity was observed in either of the 2-year bioassays conducted in mice and rats when administered via dietary admixture, at the maximally tolerated doses of 80 and 18 mg/kg/day, respectively. In mice receiving 80 mg/kg/day, mean plasma exposures in males were approximately 17-fold above the anticipated peak clinical exposure of 21.6 ng/mL at the MRHD of 10 mg b.i.d. Mean exposures in surviving females, euthanized during week 100 due to reduced survival at the 80 mg/kg/day dose level, were approximately 11-fold above the anticipated peak clinical exposure at the MRHD of 10 mg b.i.d.

Similar exposures were obtained during the 104-week carcinogenicity study in rats. Mean exposures in males at the 18 mg/kg/day dose level were approximately 17-fold above the peak exposure of 21.6 ng/mL at the MRHD of 10 mg b.i.d, and approximately 12-fold in females. A slight, non-dose-related increase in uterine polyps was observed in female rats at 18 mg/kg/day. Microscopically, an increased incidence of inflammation of the foot with secondary reaction in the regional lymph nodes and hypercellularity of the bone marrow was seen, particularly at 18 mg/kg/day.

4-Aminopyridine was not mutagenic in either the Ames bacterial mutagenicity test or in the L5178Y mouse lymphoma cell line, when tested *in vitro*. No clastogenic effects were observed either *in vitro,* when tested in Chinese Hamster Ovary (CHO) cells or *in vivo,* when tested in mice at oral doses of 9 mg/kg, or in Sprague Dawley rats at oral doses of 15 mg/kg.

No adverse effects were noted on fertility or copulatory indices in rats, and no treatment-related variations in estrous cyclicity, were attributed to 4-aminopyridine in surviving animals at doses of up to 9 mg/kg. There were no indications of developmental toxicity and no test article-related fetal malformations or developmental variations at any dosage level tested when pregnant dams were exposed to oral doses of up to 10 mg/kg/day (rat) or 5 mg/kg/day (rabbit) during the period of fetal organogenesis. Based upon data from bridging toxicokinetic studies, peak plasma exposures in pregnant rats and rabbits were greater than 23-fold above those achieved in humans at the MRHD of 10 mg b.i.d.

Effects on parturition and lactation, as evidenced from neonatal behavior, viability, growth and offspring (F1) reproductive performance, were evaluated in rats at doses of up to 6 mg/kg/day. Doses of 3 and 6 mg/kg/day were maternally toxic, as evidenced by reduced maternal food consumption and body weight during both gestation and lactation, and fewer live births were observed in pregnant dams in the 6 mg/kg dose group. Administration of 4-AP to offspring (F1) through lactation also resulted in fewer live pups per litter and reduced weight gain during and beyond lactation for animals in the 6 mg/kg dose group; however, no effects were observed at any dose level, with respect to behavior and development. Based upon data from a bridging toxicokinetic study, peak exposure levels in lactating dams were greater than 28-fold above those achieved in humans at the MRHD of 10 mg b.i.d.

Secretion of fampridine in milk has not been studied in animals.

REFERENCES

1. Albrecht H,Wötzel C, Erasmus LP, Kleinpeter M, König N, Pöllmann W. Day-to-day variability of maximum walking distance in MS patients can mislead to relevant changes in the Expanded Disability Status Scale (EDSS): average walking speed is a more constant parameter. Multiple Sclerosis 2001; 7: 105–109.

2. Cohen JA, Fischer JS, Bolibrush DM, Jak AJ, Kniker JE, et al. Intrarater and interrater reliability of the MS functional composite outcome measure. Neurology 2000;54: 802—806.

3. Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, Marinucci LN, Blight AR. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 2009;373:732-738.

4. Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, Marinucci LN, Blight AR. A Phase 3 Trial of Extended Release Oral Dalfampridine in Multiple Sclerosis. Ann Neurol 2010;68:494–502.

5. Graham RC, Hughes RAC. Clinimetric properties of a walking scale in peripheral neuropathy. J. Neurol. Neurosurg. Psychiatry 2006;77: 977–979.

6. Heesen C, Böhm J, Reich C, Kasper J, Goebel M, et al. Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. Multiple Sclerosis 2008;14: 988–991.

7. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). Neurology 2003:60: 31–36.

8. Hoogervorst ELJ, Kalkers NF, Cutter GR, Uitdehaag BMJ, Polman CH. The patient's perception of a (reliable) change in the Multiple Sclerosis Functional Composite. Mult Scler 2004;10: 55–60.

9. Kragt JJ, van der Linden FAH, Nielsen JM, Uitdehaag BMJ, Polman CH. Clinical impact of 20% worsening on Timed 25-foot Walk and 9-hole Peg Test in multiple sclerosis. Multiple Sclerosis 2006;12: 594–598.

10. McGuigan C, Hutchinson M. Confirming the validity and responsiveness of the Multiple Sclerosis Walking Scale-12 (MSWS-12). Neurology 2004;62: 2103–2105.

11. Paltamaa J, Sarasoja T, Leskinen E, Wikström J, Mälkiä E. Measures of physical functioning predict self-reported performance in self-care, mobility, and domestic life in ambulatory persons with multiple sclerosis. *Arch Phys Med Rehabil.* 2007;88:1649-1657.

12. Uges DRA, Sohn YJ, Greijdanus B, Scaf AH, Agoston S. 4-Aminopyridine kinetics. Clin Pharmacol Ther 1982; 31(5):587–593.

13. FAMPYRA™ Product Monograph, Biogen Idec Canada Inc., Date of Revision: November 26, 2014; Control no.: 177177

PART III: CONSUMER INFORMATION

[Pr]pms-FAMPRIDINE
Fampridine Sustained Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when pms-FAMPRIDINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-FAMPRIDINE. Contact your doctor or pharmacist if you have any questions about the drug.

Make sure you read and understand the section, **PROPER USE OF THIS MEDICATION.** Follow the instructions. Ask your doctor or pharmacist to explain the proper use of pms-FAMPRIDINE if you do not understand these instructions.

- **Take only one 10 mg tablet of pms-FAMPRIDINE in the morning and one 10 mg tablet in the evening, 12 hours apart.**
- **Take the tablet whole and do not divide, crush, dissolve, suck or chew the tablet.**
- **You must always leave 12 hours between each tablet. Do not take two tablets at once to make up for a missed dose. Take your next tablet when you would normally take it.**
- **Taking more than one tablet at a time or more often than every 12 hours can increase the risk of having a serious side effect, such as a seizure.**
- **If you have taken more pms-FAMPRIDINE than the prescribed dose, get emergency medical help immediately by contacting your regional Poison Control center or by calling 911. Tell them you are at risk of having a seizure after taking too much pms-FAMPRIDINE.**

ABOUT THIS MEDICATION

What the medication is:
pms-FAMPRIDINE may help adults (18 years and over) with multiple sclerosis (MS) related walking disability to walk better.

pms-FAMPRIDINE can be used alone or with other medicines used to treat MS.

Multiple sclerosis is an autoimmune disease that affects the central nervous system (CNS). The CNS is made up of the brain, nerves and spinal cord. The nerves carry electrical and chemical messages from our brain to the rest of our body – giving us the ability to think, speak and move. When nerves are damaged by MS, the normal ability for these messages to move along the nerves may be lost. This leads to the neurological symptoms such as walking difficulties, numbness, vision problems, and imbalance.

What it does:
pms-FAMPRIDINE contains the active substance fampridine, which belongs to a group of medicines called potassium channel blockers. The way that pms-FAMPRIDINE works in MS patients is not fully understood. pms-FAMPRIDINE is thought to work by blocking potassium channels, which may help messages to pass down the damaged nerve.

When it should not be used:
Do not take pms-FAMPRIDINE if you:

- Have an allergy or are sensitive to fampridine or any ingredients in this medicine (listed below).
- Are taking 4-aminopyridine (4-AP) compounded by your pharmacist.
- Have ever had a seizure (also referred to as a fit or convulsion).
- Have kidney problems.
- Are taking any other medicine containing fampridine. This may increase your risk of serious side effects.
- Are taking medicines that will reduce the elimination of pms-FAMPRIDINE from your body, which may increase your risk of serious side effects. Some of these medicines include cimetidine, and quinidine.
- Are taking other medicines that are known to increase the risk of seizures, such as bupropion, tramadol, tapentadol, or preparations used for colon cleansing.

pms-FAMPRIDINE should not be used in children and adolescents under 18 years, because it has not been studied in MS patients younger than 18 years of age.

What the medicinal ingredient is:
The active ingredient in pms-FAMPRIDINE is called fampridine.

What the nonmedicinal ingredients are:
The non-medicinal ingredients of pms-FAMPRIDINE tablets are: Colloidal Silicon Dioxide, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene glycol and Titanium Dioxide.

What dosage forms it comes in:
pms-FAMPRIDINE comes as a 10 mg sustained release tablet.

WARNINGS AND PRECAUTIONS

BEFORE you use pms-FAMPRIDINE talk to your doctor or pharmacist if:

- You have ever had a seizure. pms-FAMPRIDINE should not be used by patients who have had seizures. pms-FAMPRIDINE can increase the risk of seizures. Ask your doctor if you have any factors or if you are taking any medicines that affect your risk of seizures.
- You have kidney disease. pms-FAMPRIDINE should not be used by patients who have kidney problems.
- You have heart rhythm or conduction problems.
- You have a history of nerve pain in the face (trigeminal neuralgia).

- You are pregnant or planning to become pregnant.
- You are breastfeeding or plan to breastfeed.

Tell your doctor if you have any other medical conditions.

Before starting treatment and regularly during treatment, your doctor should check that your kidneys are working properly.

Serious allergic reactions have been observed in patients treated with fampridine. Signs of allergic reaction may include rash, itching, difficulty breathing, swelling of the face, lips, tongue or throat. In several cases, these reactions occurred after the first dose. Seek immediate emergency assistance if you develop any of these signs or symptoms.

This medicine may make you feel dizzy or unsteady and this may increase the risk of falling. If you use a walking aid, such as a cane, you should continue to use it as needed.

Risk of Seizure
It is important that you take only one 10 mg tablet of pms-FAMPRIDINE in the morning and one 10 mg tablet in the evening, 12 hours apart. Do not divide, crush, dissolve, suck or chew the tablet. Taking more than one tablet at a time or more often than every 12 hours, or taking a broken tablet can increase the risk of having a serious side effect, such as a seizure.

- If you have taken more pms-FAMPRIDINE than the prescribed dose, get emergency medical help immediately by contacting your regional Poison Control center or by calling 911. Tell them you are at risk of having a seizure after taking too much pms-FAMPRIDINE.
- If you think you missed a dose, do not take two tablets at once to make up for a missed dose. Take your next tablet when you would normally take it. You must always leave 12 hours between each tablet.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all of the medicines you take now or have taken recently, including prescription and non-prescription medicines. This includes any vitamin or mineral supplement, or herbal products.

Do not start any new medicines until you talk to your doctor who prescribed pms-FAMPRIDINE.

- 4-aminopyridine and other medicines containing fampridine: Do not take pms-FAMPRIDINE if you are taking 4-aminopyridine (4-AP, fampridine) compounded by your pharmacist. These medicines contain the same active ingredient as pms-FAMPRIDINE and should be discontinued before starting pms-FAMPRIDINE, to reduce the risk of serious side effects.
- Medicines that affect the kidneys: Your doctor will be especially careful if pms-FAMPRIDINE is given at the same time as any medicine that may affect your kidney function. Tell your doctor if you are taking medicines such as beta blockers (carvedilol, pindolol, propranolol), procainamide, metformin, ranitidine, and varenicline.

Some medicines that affect kidney function should not be taken with pms-FAMPRIDINE. Examples of these medicines include cimetidine and quinidine.

PROPER USE OF THIS MEDICATION

Always follow your doctor's instructions for taking pms-FAMPRIDINE. You should check with your doctor or pharmacist if you are not sure. **Do not take more than the prescribed dose.**

Dose:
Take one 10 mg tablet of pms-FAMPRIDINE in the morning and one tablet in the evening. **You must leave 12 hours between each tablet. Do not take a tablet more often than every 12 hours**. The tablets are to be taken without food.

Swallow each tablet whole, with a drink of water. If you cannot swallow pms-FAMPRIDINE tablets whole, tell your doctor.

Do not divide, crush, dissolve, suck or chew the tablet. A broken tablet can release too much of the drug at one time. This can increase your risk of having a seizure.

Your doctor should assess your walking ability before you start pms-FAMPRIDINE and again within the first 4 weeks of treatment. If you and your doctor decide there has not been benefit to you in this period, treatment should be stopped.

If the decision is to continue treatment, it is important that you and your doctor continue to periodically reassess whether you are experiencing benefit, and to stop taking the drug if you are not.

Overdose:
Take only the dose your doctor has prescribed you. Do not change your dose of pms-FAMPRIDINE. If you take more than your prescribed dose, there is a risk of seizure.

If you have taken too much pms-FAMPRIDINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Tell them you are at risk of having a seizure after taking too much pms-FAMPRIDINE. Take the medication package with you if you go to the hospital.

Missed Dose:
If you forget to take a tablet, **do not take two tablets at once to make up for a missed dose.** You must always leave 12 hours between each tablet.

Taking more than your prescribed dose can increase the risk of serious side effects.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, pms-FAMPRIDINE can have side effects. If you have any worrying side effects including any that are not included here, contact your doctor or pharmacist.

Seizures: Some patients have had seizures while taking pms-FAMPRIDINE, including patients who have never had seizures before. If you have a seizure while taking pms-FAMPRIDINE get emergency help right away and do not take any more pms-FAMPRIDINE.

Serious allergic reactions have been observed in patients treated with pms-FAMPRIDINE Signs of allergic reaction may include rash, itching, difficulty breathing, swelling of the face, lips, tongue or throat. In several cases, these reactions occurred after the first dose. Seek immediate emergency assistance if you develop any of these signs or symptoms.

pms-FAMPRIDINE can cause side effects. Please review the information in the table carefully.

Very common side effects (affect more than 1 in 10 patients).
Urinary tract infection

Common side effects (affect between 1 and 10 in every 100 patients).
Feeling unsteady, dizziness, headache, feeling weak and tired, difficulty sleeping, anxiety, tremor (minor shaking), numbness or tingling of the skin, sore throat, shortness of breath, feeling sick (nausea), being sick (vomiting), constipation, upset stomach, back pain.

Uncommon side effects (affect between 1 and 10 in every 1 000 patients).
Worsening of nerve pain in the face (trigeminal neuralgia).

If any of these side effects affects you severely, tell your doctor right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	In all cases	
Common (affects more than 1 in 10 patients)	Shortness of breath			✓
Uncommon (affects between 1 and 10 in every 1 000 patients)	Seizure (i.e. loss of consciousness with uncontrollable shaking)			
	Allergic reaction (symptoms include rash, itching, difficulty breathing, swelling of the face, lips, tongue or throat)			✓

This is not a complete list of side effects. For any unexpected effects while taking pms-FAMPRIDINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store pms-FAMPRIDINE at room temperature (between 15 to 30°C). Store the tablets in the original container, protected from light and moisture. pms-FAMPRIDINE is available in bottle of 60 tablets and blisters of 10 tablets. Do not take your medicine after the expiry date shown on the bottle or carton.

Keep out of reach and sight of children.

Medicines should not be disposed of in waste water or household garbage. Ask your pharmacist how to dispose of medicines you no longer need.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234 2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about pms-FAMPRIDINE:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Heath Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by:

Pharmascience Inc.
Montréal, Québec
H4P 2T4

www.pharmascience.com

Date prepared: February 10, 2020