HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMPYRA safely and effectively. See full prescribing information for AMPYRA.

AMPYRA™ (dalfampridine) Extended Release Tablets, for oral use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

AMPYRA™ (dalfampridine) is a potassium channel blocker indicated to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed (1, 14).

DOSAGE AND ADMINISTRATION

- Maximum recommended dose: 10 mg twice daily (approximately 12 hours apart) with or without food (2)
- Patients should not take double or extra doses if a dose is missed. No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse events, including seizures, were more frequent at higher doses (2)
- Tablets should only be taken whole; do not divide, crush, chew, or dissolve (2)
- Renal impairment: AMPYRA is contraindicated in patients with moderate or severe renal impairment; the risk of seizures in patients with mild renal impairment is unknown, but AMPYRA plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures (4, 5.1, 5.2)

DOSAGE FORMS AND STRENGTHS

10 mg tablets (3)

CONTRAINDICATIONS

- History of seizure (4)
- Moderate or severe renal impairment (4)

WARNINGS AND PRECAUTIONS

- Seizures: AMPYRA can cause seizures; the risk of seizures increases with increasing AMPYRA doses; AMPYRA is contraindicated in patients with a prior history of seizure; discontinue AMPYRA use if seizure occurs (5.1)
- Renally impaired patients: AMPYRA is contraindicated in patients with moderate to severe renal impairment (CrCl≤50 mL/min); the risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures (4, 5.1, 5.2); estimated CrCl should be known before initiating treatment with AMPYRA (4, 5.2, 8.6)
- AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine), since the active ingredient is the same (5.3)
- Urinary tract infections were reported more frequently as adverse reactions in patients receiving AMPYRA 10 mg twice daily compared to placebo (5.4)

ADVERSE REACTIONS

The most common adverse events (incidence ≥2% and at a rate greater than the placebo rate) for AMPYRA in MS patients were urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Acorda Therapeutics at 1-800-367-5109 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

None identified.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric use: Safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established
- Renal Impairment: Clearance of dalfampridine is decreased in patients with renal impairment; AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl≤50 mL/min); AMPYRA plasma levels in patients with mild renal impairment (CrCl 51–80 mL/min) may approach those seen at a dose of 15 mg twice daily, a dose which may be associated with an increased risk of seizures (4, 5.2, 8.6)
- Geriatric use: Because elderly patients are more likely to have decreased renal function, it is particularly important to know the estimated CrCl in these patients before initiating AMPYRA treatment (4, 5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMPYRA (dalfampridine) is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The maximum recommended dose of AMPYRA is one 10 mg tablet twice daily, taken with or without food, and should not be exceeded. Doses should be taken approximately 12 hours apart. Patients should not take double or extra doses if a dose is missed.

No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse reactions and discontinuations because of adverse reactions were more frequent at higher doses. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.

AMPYRA is contraindicated in patients with moderate or severe renal impairment *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma exposure in these patients may approach that seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures; estimated CrCl should be known before initiating treatment with AMPYRA *[see Warnings and Precautions, Renal Impairment (5.2) and Clinical Pharmacology, Special Populations (12.4)]*.

[See FDA-Approved Patient Information for complete "Instructions for Use"]

3 DOSAGE FORMS AND STRENGTHS

AMPYRA is available in a 10 mg strength and is a film-coated, white to off-white, biconvex, oval shaped, non-scored tablet with flat edge, debossed with "A10" on one side.

4 CONTRAINDICATIONS

The use of AMPYRA is contraindicated in the following conditions:

- History of seizure
- Moderate or severe renal impairment

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

AMPYRA is contraindicated in patients with a history of seizures *[see Contraindications (4)]*. Increased incidence of seizures has been observed at 20 mg twice daily in controlled clinical studies of 9–14 weeks duration with dalfampridine in patients with MS. There was one seizure seen in the placebo group (0.4%) and at a dose of 10 mg twice daily (0.25%), no seizure seen at 15 mg twice daily and 2 seizures (3.5%) seen at 20 mg twice daily. In open label extension trials in MS patients, the incidence of seizures during treatment with dalfampridine 15 mg twice daily (1.7/100PY) was over 4 times higher than the incidence during treatment with 10 mg twice daily (0.4/100PY).

AMPYRA has not been evaluated in patients with a history of seizures or with evidence of epileptiform activity on an EEG, as these patients were excluded from clinical trials. The risk of seizures in patients with epileptiform activity on EEG is unknown, and could be substantially higher than that observed in AMPYRA clinical studies. AMPYRA should be discontinued and not restarted in patients who experience a seizure while on treatment.

5.2 Renal Impairment

AMPYRA is eliminated through the kidneys primarily as unchanged drug *[see Clinical Pharmacology, Special Populations (12.4)]*.

Because patients with renal impairment would require a dose lower than 10 mg twice daily and no strength smaller than 10 mg is available, AMPYRA is contraindicated in patients with moderate to severe renal impairment [Creatinine Clearance (CrCl) ≤50mL/min] *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but dalfampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures *[see Warnings and Precautions, Seizures (5.1)]*. If unknown, CrCl should be estimated prior to initiating treatment with AMPYRA. CrCl can be estimated using the following equation (multiply by 0.85 for women):

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

5.3 Concurrent Treatment with Other Forms of 4-Aminopyridine

AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine) since the active ingredient is the same. Patients should discontinue use of any product containing 4-aminopyridine prior to initiating treatment with AMPYRA in order to reduce the potential for dose-related adverse reactions.

5.4 Urinary Tract Infections

Urinary tract infections were reported more frequently as adverse reactions in controlled studies in patients receiving AMPYRA 10 mg twice daily (12%) as compared to placebo (8%).

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label: Seizures and Urinary Tract Infections.

6.1 Controlled Clinical Trials Experience

In three placebo-controlled clinical trials of up to 14 weeks duration, 4% (15/400) of patients treated with AMPYRA 10 mg twice daily experienced one or more treatment emergent adverse events leading to discontinuation, compared to 2% (5/238) of placebo-treated patients. The treatment emergent adverse events leading to discontinuation of at least 2 patients treated with AMPYRA and that led to discontinuation more frequently compared to placebo were headache (AMPYRA 0.5%, placebo 0%), balance disorder (AMPYRA 0.5%; placebo 0%), dizziness (AMPYRA 0.5%, placebo 0%), and confusional state (AMPYRA 0.3%, placebo 0%).

Table 1 lists adverse reactions that occurred in ≥2% of patients treated with AMPYRA 10 mg twice daily, and more frequently than in placebo-treated patients, in controlled clinical trials.

Table 1: Adverse reactions with an incidence ≥2% of AMPYRA treated MS patients, and more frequent with AMPYRA compared to placebo in controlled clinical trials

Adverse Reaction	Placebo (N=238)	AMPYRA 10 mg twice daily (N=400)
Urinary tract infection	8%	12%
Insomnia	4%	9%
Dizziness	4%	7%
Headache	4%	7%
Nausea	3%	7%
Asthenia	4%	7%
Back pain	2%	5%
Balance disorder	1%	5%
Multiple sclerosis relapse	3%	4%
Paresthesia	3%	4%
Nasopharyngitis	2%	4%
Constipation	2%	3%
Dyspepsia	1%	2%
Pharyngolaryngeal pain	1%	2%

6.2 Other Adverse Reactions

AMPYRA has been evaluated in a total of 1,952 subjects, including 917 MS patients. A total of 741 patients have been treated with AMPYRA for over six months, 501 for over one year and 352 for over two years. The experience in open-label clinical trials is consistent with the safety profile observed in the placebo-controlled clinical trials. As in controlled clinical trials, a dose-dependent increase in the incidence of seizures has been observed in open-label clinical trials with AMPYRA in patients with MS as follows: AMPYRA 10 mg twice daily 0.41 per 100 person-years (95% confidence interval 0.13–0.96); dalfampridine 15 mg twice daily 1.7 per 100 person-years (95% confidence interval 0.21–6.28).

7 DRUG INTERACTIONS

In humans, dalfampridine is eliminated predominately unchanged by the kidneys. No clinically significant drug interaction was identified *[see Clinical Pharmacology, Pharmacokinetics (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of AMPYRA in pregnant women. Administration of dalfampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses similar to the maximum recommended human dose (MRHD) of 20 mg/day. AMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in rats and rabbits, dalfampridine was administered orally at doses up to 10 and 5 mg/kg/day, respectively, during the period of organogenesis. These doses are approximately 5 times the MRHD on a body surface area (mg/m^2) basis. No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. Oral administration of dalfampridine (at doses of 1, 3, and 9/6 mg/kg/day; high dose reduced during the second week of dosing) to rats throughout the pregnancy and lactation periods resulted in decreased offspring survival and growth. The no-effect dose for pre- and postnatal developmental toxicity in rats (1 mg/kg) is approximately 0.5 times the MRHD on a mg/m^2 basis.

8.2 Labor and delivery
The effect of AMPYRA on labor and delivery in humans is unknown.

8.3 Nursing mothers
It is not known whether dalfampridine 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 dalfampridine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric use
Safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established.

8.5 Geriatric use
Clinical studies of AMPYRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. A population PK analysis showed that dalfampridine clearance modestly decreased with increasing age, but not sufficiently to necessitate a modification of dose with age. Other reported clinical experience has identified no differences in responses between the elderly and younger patients.

AMPYRA is known to be substantially excreted by the kidney and the risk of adverse reactions, including seizures, is greater with increasing exposure of dalfampridine. Because elderly patients are more likely to have decreased renal function, it is particularly important to know the estimated creatinine clearance (CrCl) in these patients *[see Warnings and Precautions, Renal Impairment (5.2)]*.

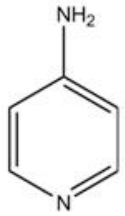
8.6 Impaired Renal Function
Clearance of dalfampridine is decreased in patients with renal impairment and is significantly correlated with creatinine clearance *[see Clinical Pharmacology, Special Populations (12.4)]*. AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl ≤50 mL/min) *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but dalfampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures. Creatinine clearance (CrCl) should be calculated prior to initiating treatment with AMPYRA *[see Warnings and Precautions, Renal Impairment (5.2)]*.

9 DRUG ABUSE AND DEPENDENCE
No studies on the abuse or dependence potential of AMPYRA have been performed.

10 OVERDOSAGE
Three cases of overdose were reported in controlled clinical trials with AMPYRA, 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, she experienced a complex partial seizure and, in the second instance, a period of confusion. Both patients recovered by the following day without sequelae.

Several cases of overdose are found in the scientific literature in which various formulations of dalfampridine were used, resulting in numerous 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. In one published case report, an MS patient who ingested 300 mg of 4-aminopyridine (dalfampridine) developed a condition that resembled limbic encephalitis. This patient developed weakness, reduced awareness, memory loss, hypophonic speech, and temporal lobe hyperintensities on MRI. The patient's speech and language and ambulation improved over time, and an MRI at 4 months after the overdose no longer showed signal abnormalities. At one year, the patient continued to have difficulty with short term memory and learning new tasks.

11 DESCRIPTION
AMPYRA (dalfampridine) is a potassium channel blocker, available in a 10 mg tablet strength. Each tablet contains 10 mg dalfampridine, formulated as an extended release tablet for twice-daily oral administration. Dalfampridine is also known by its chemical name, 4-aminopyridine, with the following structure:



AMPYRA (dalfampridine) Extended Release tablets are available in a 10 mg strength and are a white to off-white, biconvex, oval shaped, film-coated, non-scored tablet with flat edge, debossed with "A10" on one side, containing 10 mg of dalfampridine. Inactive ingredients consist of colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Dalfampridine is a fine white powder with a molecular weight of 94.1, CAS 504-24-5 and a molecular formula of $C_5H_6N_2$. At ambient conditions, dalfampridine is soluble in water, methanol, acetone, tetrahydrofuran, isopropanol, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, and ethanol.

12 CLINICAL PHARMACOLOGY

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

12.2 Pharmacodynamics
AMPYRA does not prolong the QTc interval and does not have a clinically important effect on QRS duration.

12.3 Pharmacokinetics
Absorption and Distribution:
Orally administered dalfampridine is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of extended release AMPYRA tablets has not been assessed, but relative bioavailability is 96% when compared to an aqueous oral solution. The extended release tablet delays absorption of dalfampridine relative to the solution formulation, giving a slower rise to a lower peak concentration (Cmax), with no effect on the extent of absorption (AUC). Single AMPYRA tablet 10 mg doses administered to healthy volunteers in a fasted state gave peak concentrations ranging from 17.3 ng/mL to 21.6 ng/mL occurring 3 to 4 hours post-administration (Tmax). In comparison, Cmax with the same 10 mg dose of dalfampridine in an oral solution was 42.7 ng/mL and occurred approximately 1.3 hours after dosing. Exposure increased proportionally with dose.

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

There is no apparent difference in pharmacokinetic parameter values following administration of AMPYRA tablets to either healthy volunteers or patients with MS.

When dalfampridine is taken with food, there is a slight increase in Cmax (12–17%) and a slight decrease in AUC (4–7%). These changes in exposure are not clinically significant, and therefore the drug may be taken with or without food *[see Dosage and Administration (2)]*.

Metabolism and Elimination:
Dalfampridine and metabolites elimination is nearly complete after 24 hours, with 95.9% of the dose recovered in urine and 0.5% recovered in feces. Most of the excreted radioactivity in urine was parent drug (90.3%). Two metabolites were identified: 3-hydroxy-4-aminopyridine (4.3%) and 3-hydroxy-4-aminopyridine sulfate (2.6%). These metabolites have been shown to have no pharmacologic activity on potassium channels.

The elimination half-life of dalfampridine following administration of the extended release tablet formulation of AMPYRA 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.

In vitro studies with human liver microsomes indicate that CYP2E1 was the major enzyme responsible for the 3-hydroxylation of dalfampridine. The identity of the CYP enzymes suspected of playing a minor role in the 3-hydroxylation of dalfampridine could not be established unequivocally.

12.4 Special Populations

Pediatric
The safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established.

Geriatric
A population pharmacokinetic analysis showed that dalfampridine clearance modestly decreased with increasing age, but not sufficiently to necessitate a modification of dose.

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

Renal Impairment *[see Contraindications (4) and Warnings and Precautions, Renal Impairment (5.2)]*.
The pharmacokinetics of dalfampridine 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 dalfampridine was reduced by about 45 % in patients with mild renal impairment (CrCl 51–80 mL/min), by about 50% in patients with moderate renal impairment (CrCl = 30–50 mL/min), and by about 75% in patients with severe renal impairment (CrCl <30 mL/min). The terminal half-life of dalfampridine is about 3.3 times longer in patients with severe renal impairment but is not prolonged in patients with mild or moderate renal impairment.

Hepatic Impairment
The pharmacokinetics of dalfampridine in hepatically impaired subjects has not been studied. Since dalfampridine is primarily excreted unchanged in the urine, hepatic impairment is not expected to significantly affect dalfampridine pharmacokinetics or recommended dosing.

Race
There were too few non-Caucasians in the patient population to evaluate the effect of race.

Drug Interactions
Effects of Coadministered Drugs on Dalfampridine
Interferon
Dalfampridine kinetics were not affected by co-administration of subcutaneous injections of 8 million units interferon beta-1b.

Baclofen
No pharmacokinetic drug-drug interaction was observed with co-administration of dalfampridine 15 mg and baclofen 10 mg.

Effects of Dalfampridine on Coadministered Drugs
In vitro data with human liver microsomes showed that dalfampridine was not a direct or time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of these enzymes.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Two year dietary carcinogenicity studies of dalfampridine were conducted in mice and rats. In mice, the doses tested (approximately 2, 12.5, and 80 mg/kg/day) were associated with plasma exposures (AUC) up to 18 times the plasma AUC in humans at the maximum recommended human dose (MRHD) of 20 mg/day. There was no evidence of drug-related carcinogenicity.

In rats, the doses tested (approximately 2, 6, and 18 mg/kg/day) were approximately 1, 3, and 9 times the MRHD on a body surface area (mg/m^2) basis. There was a significant increase in uterine polyps at the highest dose tested.

Mutagenesis*:* Dalfampridine was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma *tk*, chromosomal aberration) and *in vivo (*mouse bone marrow, rat erythrocyte micronucleus) genetic toxicology assays.

Impairment of Fertility: Oral administration of dalfampridine (doses of 1, 3, and 9 mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females up to day 13 of gestation or day 21 of lactation resulted in no adverse effects on fertility. Reduced offspring viability and body weight were observed at 9 mg/kg/day. The mid dose (a no-effect dose) was similar to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

The effectiveness of AMPYRA in improving walking in patients with multiple sclerosis was evaluated in two adequate and well controlled trials involving 540 patients. Patients in these two clinical trials had a mean disease duration of 13 years and a mean Kurtzke Expanded Disability Status Scale (EDSS) score of 6.

Trial 1 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 AMPYRA 10 mg twice daily and 72 patients assigned to placebo. A total of 283 patients (212 AMPYRA and 71 placebo) completed all study visits. Patient inclusion criteria included the ability to walk 25 feet in 8–45 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.

Trial 2 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 AMPYRA and 114 placebo) completed all study visits. The patient inclusion and exclusion criteria used in Trial 1 were employed in Trial 2, and in addition patients with severe renal impairment were also excluded.

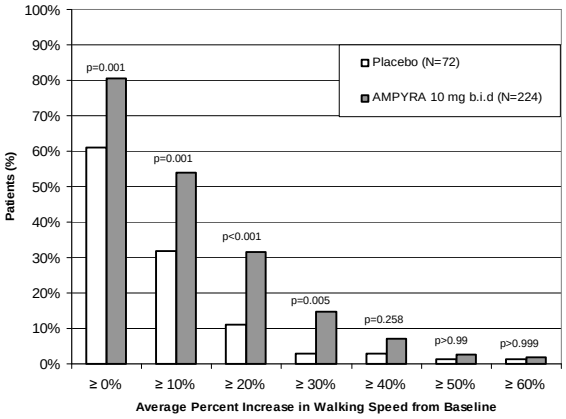
The primary measure of efficacy in both trials was walking speed (in feet per second) as measured by the Timed 25-foot Walk (T25W), using a responder analysis. A responder was defined as a patient who showed faster walking speed for a least three visits out of a possible four during the double-blind period than the maximum value achieved in the five non-double-blind no treatment visits (four before the double-blind period and one after).

A significantly greater proportion of patients taking AMPYRA 10 mg twice daily were responders, compared to patients taking placebo, as measured by the T25FW (Trial 1: 34.8% vs. 8.3%; Trial 2: 42.9% vs. 9.3%). The increased response rate in the AMPYRA 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 AMPYRA 10 mg twice daily had increases in walking speed

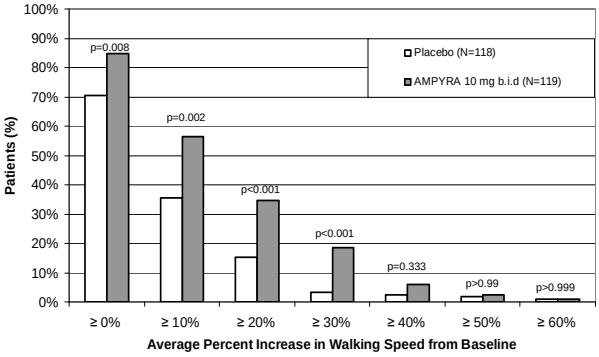
of at least 10%, 20%, or 30% from baseline, compared to placebo (Figure 1 and Figure 2).

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



P values provided at each threshold comparing AMPYRA to placebo.

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



P values provided at each threshold comparing AMPYRA to placebo.

In Trial 1 and Trial 2, 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. However, a drug-placebo difference was not established for that outcome measure.

The majority of patients in these trials (63%) were using immunomodulatory drugs (interferons, glatiramer acetate, or natalizumab), but the magnitude of improvement in walking ability was independent of concomitant treatment with these drugs. No differences in effectiveness 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

AMPYRA (dalfampridine) extended release tablets, 10 mg are a film-coated, white to off-white, biconvex, oval shaped, non-scored tablets with flat edge. The tablets are identified by a debossed code “A10” on one side and are available in bottles of 60.

- NDC 10144-427-60 bottles of 60 tablets

Store at 25°C (77°F). Excursions permitted 15–30ºC (59–86ºF).

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Risk of Seizures

Inform patients that AMPYRA causes seizures in a dose-dependent fashion, and that they must discontinue use of AMPYRA if they experience a seizure.

17.2 AMPYRA dosing

Instruct patients to take AMPYRA exactly as prescribed. Instruct patients not to take a double dose after they miss a dose. Instruct patients not take more than 2 tablets in a 24-hour period and to make sure that there is an approximate 12-hour interval between doses.

17.3 Storage

Advise patients to store AMPYRA at 25°C (77°F), with excursions permitted to 15–30ºC (59–86ºF). Advise patients to safely throw away AMPYRA that is out of date or no longer needed.

FDA-Approved Patient Labeling

MEDICATION GUIDE FOR
AMPYRA™ (am-PEER-ah)
(dalfampridine) Extended Release Tablets
Read this Medication Guide before you start taking AMPYRA.

Read this Medication Guide before you start taking AMPYRA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about AMPYRA?
AMPYRA can cause seizures.
- Your chance of having a seizure is higher if you take too much AMPYRA or if you have kidney problems.
- Do not take AMPYRA if you have ever had a seizure.
- Before taking AMPYRA tell your doctor if you have kidney problems.
- Take AMPYRA exactly as prescribed by your doctor. See "How do I take AMPYRA?"

Stop taking AMPYRA and call your doctor right away if you have a seizure while taking AMPYRA.

What is AMPYRA?
AMPYRA is a prescription medicine used to help improve walking in people with multiple sclerosis (MS). This was shown by an increase in walking speed.
It is not known if AMPYRA is safe or effective in children less than 18 years of age.

Who should not take AMPYRA?
Do not take AMPYRA if you:
- have ever had a seizure
- have certain types of kidney problems

What should I tell my doctor before taking AMPYRA?
Before you take AMPYRA, tell your doctor if you:
- have any other medical conditions
- are taking compounded 4-aminopyridine (fampridine, 4-AP)
- are pregnant or plan to become pregnant. It is not known if AMPYRA will harm your unborn baby. You and your doctor will decide if you should take AMPYRA while you are pregnant
- are breast-feeding or plan to breast-feed. It is not known if AMPYRA passes into your breast milk. You and your doctor should decide if you will take AMPYRA or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take AMPYRA?
- Take AMPYRA exactly as your doctor tells you to take it. Do not change your dose of AMPYRA.
- Take one tablet of AMPYRA 2 times each day about 12 hours apart. Do not take more than 2 tablets of AMPYRA in a 24-hour period.
- Take AMPYRA tablets whole. Do not break, crush, chew or dissolve AMPYRA tablets before swallowing. If you cannot swallow AMPYRA tablets whole, tell your doctor.
- AMPYRA is released slowly over time. If the tablet is broken, the medicine may be released too fast. This can raise your chance of having a seizure.
- AMPYRA can be taken with or without food.
- If you miss a dose of AMPYRA, do not make up the missed dose. Do not take 2 doses at the same time. Take your next dose at your regular scheduled time.
- If you take too much AMPYRA, call your doctor or go to the nearest hospital emergency room right away.
- Do not take AMPYRA together with other aminopyridine medications, including compounded 4-AP (sometimes called 4-aminopyridine, fampridine).

What are the possible side effects of AMPYRA?
AMPYRA may cause serious side effects, including:
- Kidney or bladder infections

See "What is the most important information I should know about AMPYRA?"

The most common side effects of AMPYRA include:
- urinary tract infection
- trouble sleeping (insomnia)
- dizziness
- headache
- nausea
- weakness
- back pain
- problems with balance
- multiple sclerosis relapse
- burning, tingling or itching of your skin
- irritation in your nose and throat

- constipation
- indigestion
- pain in your throat

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of AMPYRA. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store AMPYRA?

- Store AMPYRA at 59ºF to 86ºF (15ºC to 30ºC).
- Safely throw away AMPYRA that is out of date or no longer needed.

Keep AMPYRA and all medicines out of the reach of children.

General Information about the safe and effective use of AMPYRA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMPYRA for a condition for which it was not prescribed. Do not give AMPYRA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about AMPYRA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AMPYRA that is written for health professionals.
For more information, go to www.AMPYRA.com or call 1-800-367-5109.

What are the ingredients in AMPYRA?
Active ingredient: dalfampridine (previously called fampridine)
Inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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