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

- The maximum recommended dose is 10 mg twice daily (approximately 12 hours apart), with or without food. **Tablets should only be taken whole; do not divide, crush, chew, or dissolve** (2)
- Estimated creatinine clearance (CrCl) should be known before initiating treatment with AMPYRA. In patients with mild renal impairment (CrCl 51–80 mL/min), AMPYRA may reach plasma levels associated with a greater risk of seizures, and the potential benefits of AMPYRA should be carefully considered against the risk of seizures in these patients (2, 5.2, 8.6)
- 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)

DOSAGE FORMS AND STRENGTHS

10 mg tablets (3)

CONTRAINDICATIONS

- History of seizure (4)
- Moderate or severe renal impairment (CrCl≤50 mL/min) (4)
- History of hypersensitivity to AMPYRA or 4-aminopyridine (4)

WARNINGS AND PRECAUTIONS

- AMPYRA can cause seizures; the risk of seizures increases with increasing AMPYRA doses; discontinue AMPYRA and do not restart if a seizure occurs (5.1)
- AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine), since the active ingredient is the same (5.3)
- AMPYRA can cause anaphylaxis. Discontinue and do not restart AMPYRA if this occurs (5.4)

ADVERSE REACTIONS

The most common adverse events (incidence ≥2% and at a rate greater than the placebo rate) for AMPYRA 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 (7)

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)
- 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: 12/2014

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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. **Tablets should only be taken whole; do not divide, crush, chew, or dissolve.** Patients should not take double or extra doses if a dose is missed.

Estimated creatinine clearance (CrCl) should be known before initiating treatment with AMPYRA, and monitored at least annually during treatment with AMPYRA. CrCl can be estimated using the following equation (multiply by 0.85 for women):

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

In patients with mild renal impairment (CrCl 51–80 mL/min), AMPYRA plasma levels may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures. As mild renal impairment is common after age 50, estimating CrCl is particularly important in these patients. The potential benefits of AMPYRA should be carefully considered against the risk of seizures in these patients *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.4)]*.

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 *[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 (CrCl≤50 mL/min)
- History of hypersensitivity to AMPYRA or 4-aminopyridine

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

AMPYRA can cause seizures. 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. 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). In the post-marketing period seizures have been reported. The majority of seizures occurred at the recommended dose and in patients without a history of seizures, and generally within days to weeks of starting therapy.

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 an 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. AMPYRA is contraindicated in patients with a history of seizures *[see Contraindications (4)]*.

5.2 Renal Impairment

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

Because patients with moderate to severe renal impairment (CrCl ≤50mL/min) would require a dose lower than 10 mg twice daily and no strength smaller than 10 mg is available, AMPYRA is contraindicated in these patients *[see Contraindications (4)]*.

In patients with mild renal impairment (CrCl 51–80 mL/min), AMPYRA plasma levels 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 (5.1)]*.

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 Anaphylaxis

AMPYRA can cause anaphylaxis and severe allergic reactions. Signs and symptoms have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Patients should be informed of the signs and symptoms of anaphylaxis and instructed to discontinue AMPYRA and seek immediate medical care should these signs and symptoms occur (17.3).

5.5 Urinary Tract Infections

Urinary tract infections (UTIs) were reported more frequently as adverse reactions in controlled studies in patients receiving AMPYRA 10 mg twice daily (12%) as compared to placebo (8%). UTIs in AMPYRA-treated patients should be evaluated and treated as clinically indicated.

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 reactions are described in more detail in the Warnings and Precautions section of the label: Seizures, Anaphylaxis, 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 predominantly unchanged by the kidneys. No clinically significant drug interaction was identified. In particular, no interaction was identified between dalfampridine and baclofen *[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 to 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 than 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.

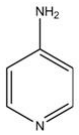
AMPYRA is known to be substantially excreted by the kidneys and the risk of adverse reactions, including seizures, is greater with increasing exposure of dalfampridine. Because elderly patients are more likely to have decreased renal function, it is particularly important to know the estimated creatinine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

8.6 Impaired Renal Function
Clearance of dalfampridine is decreased in patients with renal impairment and is significantly correlated with creatinine clearance (CrCl) *[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. If unknown, estimated creatinine clearance should be calculated prior to initiating treatment with AMPYRA *[see Dosage and Administration (2) and Warnings and Precautions (5.2)]*.

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 white to off-white, biconvex, oval shaped, film-coated, non-scored tablets 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

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 apparent 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 Co-administered Drugs on Dalfampridine
Interferon
Dalfampridine kinetics were not affected by co-administration of subcutaneous injections of 8 million units interferon beta-1b.

Baclofen
Based on a population analysis, dalfampridine kinetics were not affected by baclofen.

Effects of Dalfampridine on Co-administered 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.

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