

NEW DRUG UPDATE

Drug Name:	dalfampridine
Trade Name (Manufacturer):	Ampyra® (Acorda Therapeutics, Inc.)
Form:	Extended release tablet
Strength:	10 mg
FDA Approval:	January 22, 2010
Market Availability:	March 2010
FDA Approval Classification:	Standard review
Classification:	Specific Therapeutic Class (HIC3): Agents for the treatment of neuromuscular transmission disorders, potassium channel blocker (H0F)

Indication:¹ Dalfampridine (Ampyra), a potassium channel blocker, is indicated to improve walking in patients with multiple sclerosis (MS). This compound has been previously referred to as fampridine sustained release (SR) and 4-aminopyridine. To eliminate potential name confusion with other marketed drugs the generic name (fampridine) was changed to dalfampridine on January 22, 2010.² The formulation of the product has not changed. In this review, the generic name dalfampridine will be used to refer to this drug.

Background: Dalfampridine is an organic compound belonging to the chemical class of pyridine compounds. This compound is available commercially as a pesticide for birds. In addition, although the compound has no prior approval for any indication, it has been compounded in pharmacies and used off-label to improve walking in a number of neurological conditions for over 20 years. Neurological conditions where dalfampridine has been used include spinal cord injury, Guillain-Barre syndrome and multiple sclerosis. Of note, the compounded product is an immediate-release formulation and the commercial product (Ampyra®) is a sustained release product. Prescribers of the newly approved extended-release formulation should assure that patients are not concurrently taking any other formulation of this drug.^{10,11}

Clinical Pharmacology/Pharmacokinetics: Dalfampridine is a selective potassium channel blocker thought to improve conduction of action potential in demyelinated nerves. The mechanism by which dalfampridine exerts its clinical effect has not been fully elucidated. It is proposed that as a result of improved conduction, more impulses are transmitted down the axon, transmission of motor impulses between affected brain regions and between brain and spinal cord increase. Increased transmission potentially increases activation of lower motor neurons and output to muscle fibers that in turn lead to increased muscle strength as well as improvements in sensory and coordination functions involved in walking.^{1,10}

Dalfampridine is rapidly absorbed following oral administration of the extended-release product with peak concentrations occurring at 3 to 4 hours. It is highly bound to plasma protein (97% to 99%) and is predominantly eliminated unchanged by the kidney. Clearance is correlated to creatinine clearance (CrCl). The elimination half-life is approximately 5.2 to 6.5 hours in patients with normal renal function. Total body clearance is reduced by approximately 45% and 50% in patients with mild (CrCl 51-80 mL/min) to moderate (CrCl 30 to 50 mL/min) renal impairment, respectively, but half-life is not significantly prolonged. In patients with severe renal impairment, clearance is reduced by approximately 75% and half-life increases by approximately three-fold.^{1,11}

Contraindications/Warnings: Dalfampridine is contraindicated in patients with a history of seizures or moderate or severe renal impairment (creatinine clearance [CrCL] \leq 50mL/min). Use of dalfampridine can cause seizures, including generalized tonic-clonic seizures. The incidence of seizure is dose related. The maximum recommended dosage is 10 mg twice daily.^{1,10}

Urinary tract infections were reported more frequently in patients receiving dalfampridine as compared to placebo.^{1,10}

As part of a Risk Evaluation and Mitigation Strategy (REMS) to reduce the potential risk of drug associated seizures Acorda is required to inform practitioners and patients about the serious risks associated with dalfampridine therapy.

A Patient Service Hub has also been created as an initial contact between the patient and prescriber. The role of the Service Hub is to triage all patients receiving dalfampridine to a limited network of Specialty Pharmacies. The specialty pharmacy will dispense the medication and provide the patient with counseling and a medication guide. The specialty pharmacy will also be required to reinforce the recommended dosage of 10 mg twice daily. The pharmacist will contact the prescriber to verify any total daily doses exceeding 20 mg.

Drug Interactions: No drug interactions have been identified.

Common Adverse Effects: The most common adverse effects occurring in clinical trials included (in order of decreasing incidence) urinary tract infection (12 percent), insomnia (nine percent), dizziness, headache, nausea, asthenia (seven percent each), back pain, balance disorder (five percent each), MS relapse, paresthesia, nasopharyngitis (four percent), constipation (three percent), dyspepsia, and pharyngolaryngeal pain (two percent each).

Special Populations:

Pediatrics: The safe and effective use of dalfampridine in pediatrics (patients under 18 years of age) has not been established.

Pregnancy: Pregnancy Category C

Renal impairment: In patients with moderate to severe renal impairment (CrCL \leq 50 mL/min), use of dalfampridine is contraindicated.

Hepatic impairment: The use of dalfampridine in patients with hepatic impairment has not been studied.

Geriatrics: Estimation of CrCL is recommended before starting dalfampridine since elderly may be more likely to have decreased renal function.

Dosages: Dalfampridine is dosed one tablet twice daily taken approximately twelve hours apart with or without food. Higher doses are not recommended due to an increase in seizure risk.

Clinical Trials: A literature search was performed using “dalfampridine” and “fampridine SR”. Dalfampridine was studied in a randomized, placebo-controlled, parallel group trial over 21 weeks.^{3,10} The 21 weeks were as follows: one week post screening, two weeks, single-blind

placebo run-in, 14 weeks double-blind treatment and four weeks no treatment follow-up. The study included 301 patients with MS that received either dalfampridine 10 mg twice daily (229 patients) or placebo (72 patients). Inclusion criterion included the ability to walk 25 feet in 8 to 45 seconds. Patients who had a history of seizures or onset of an MS exacerbation within 60 days were excluded from the trial. Walking speed (in feet per second) as measured by the Timed 25-Foot walk was the primary measure of efficacy. A responder was defined as a patient who showed faster walking speed for at least 3 visits out of a possible 4 during the double-blind period, compared with the maximum value achieved during visits before and after study drug. Response was achieved in 34.8% of patients receiving dalfampridine versus 8.3% of patients randomized to placebo ($p < 0.001$). The average change from baseline in walking speed for dalfampridine responders was 25.2% (0.51 ft/sec), compared with an increase of 4.7% (0.1 ft/sec) in the placebo group. The difference between dalfampridine non-responders and placebo was not significant ($p = 0.5$). A 20 percent or greater improvement in walking speed was considered clinically meaningful.^{4,5,6}

In a second randomized, placebo-controlled, parallel group a 14 week trial with 239 patients with MS, the results were comparable.⁷ The weeks were as follows: one week post screening, two weeks, single-blind placebo run-in, nine weeks double-blind treatment and two weeks no treatment follow-up. A total of 120 patients were assigned to dalfampridine, and 110 patients were assigned to placebo. A significantly greater number of patients taking dalfampridine showed an improvement in walking speed (42.9 percent) versus placebo (9.3 percent: $p < 0.001$). the difference between non-responders and placebo-treated patients was not significant. The mean change in walking speed from baseline to last double-blind visit was: responders = 0.56 ft/sec; non-responders = 0.10 ft/sec; placebo = 0.19 ft/sec. The FDA conducted an ad hoc analysis of walking speed change from baseline to last double-blind assessment. They report that responder's walking speed increased from 2.29 ft/sec to 2.73 ft/sec for a change of 0.44 ft/sec. For non-responders the increase in walking speed was 2.23 ft/sec at baseline and 2.30 ft/sec at last on treatment visit, for a change of 0.07 ft/sec.^{10,11}

In both trials the majority of the patients (63 percent) were using immunomodulatory medications, but study outcomes were independent of concomitant treatment with these medications.

Other Drugs Used for Condition: Dalfampridine (Ampyra) is the first FDA-approved medication indicated to improve walking in MS patients. Other MS approved medications such as Interferon beta (Avonex[®], Betaseron[®], Extavia[®], and Rebif[®]), glatiramer acetate (Copaxone[®]) and natalizumab (Tysabri[®]) are indicated to decrease relapse rates or delay progression of the disease.

Place in Therapy: Dalfampridine (Ampyra) offers the first oral medication to improve walking in patients with MS. Improvements in walking speed occurred in the minority of studied patients and on average appear to be modest. The most recent version of the evidence based guidelines of the American Academy of Neurology (AAN) and the MS Council for Clinical Practice Guidelines (issued in 2002 and last reaffirmed in July 2008) do not address the use of dalfampridine (Ampyra).⁸⁹ Given the drug targets walking speed, it is recommended that it be used as add-on therapy to agents that modify progression of disease in MS patients.

References:

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- ⁸ Goodin DS, Frohman EM, Garmany GP Jr, Halper J, Likosky WH, Lublin FD, Silberberg DH, Stuart WH, van den Noort S. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002 Jan 22; 58(2):169-78.
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- ¹¹ Katz RG. Fampridine Sustained Release. Summary Review, Center for Drug Evaluation and Research available at www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000TOC.cfm