

Brand Name: Ampyra™

Generic Name: Dalfampridine

Manufacturer^{3,8}: Acorda Therapeutics, Inc.

Drug Class¹⁻⁸: Potassium Channel Blocker

Uses^{1,2,3,4}:

Labeled Uses: Treatment to improve walking in multiple sclerosis (MS) patients

Unlabeled Uses²: Acute spinal cord injury, Disorder of neuromuscular transmission

Mechanism of Action^{1,2,3,4}:

Nonspecific potassium channel blocker which improves conduction in focally demyelinated axons by delaying repolarization and prolonging the duration of action potentials. Enhanced neuronal conduction is thought to strengthen skeletal muscle fiber twitch activity, thereby, improving peripheral motor neurologic function.

Pharmacokinetics^{1,2,3,4,7}:

Absorption:

T_{MAX}	3-4 hours
V_d	2.6 L/kg
$t_{1/2}$	5-7 hours; prolonged in severe renal impairment (~3 times longer)
Clearance	N/A
Protein binding	Negligible
Bioavailability	96%

Metabolism: The CYP2E1 isoenzyme is the major enzyme responsible for the 3-hydroxylation of dalfampridine.

Elimination: Of an administered dose, 95.9% is recovered in the urine within 24 hours and 0.5% is excreted in the feces; 90.3% of the drug in the urine is parent drug. Two inactive metabolites are present: 3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulfate.

Efficacy:

Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, Cohen R, Marinucci LN, Blight AR; Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology*. 2008 Oct 7;71(15):1134-41.⁵

Study Design: Multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study

Description of Study:

Methods: 206 participants at 24 centers in the United States and Canada were included in the study. Participants were randomly assigned to receive fampridine (10, 15, or 20 mg twice daily) or placebo for 15 weeks. The primary outcome was percent change in walking speed during treatment relative to baseline. Secondary outcomes included the Lower Extremity Manual Muscle Test (LEMMT), Ashworth Score for spasticity, a Clinician (CGI) and Subject Global Impression (SGI), the Multiple Sclerosis Quality of Life Inventory (MSQLI), the 12-Item Multiple Sclerosis Walking Scale (MSWS-12), and the other Multiple Sclerosis Functional Composite (MSFC) components, the Nine-Hole Peg Test (9HPT) and Paced Auditory Serial Addition Test (PASAT). AEs, EKG, clinical laboratory results, vital signs, and physical examination were used to assess safety.

Outcome Results: There was no significant difference between any of the treatment groups and placebo in terms of T25FW, although all three groups treated with fampridine showed larger increases in walking speed than the placebo group. There were improvements compared with placebo in mean LEMMT score during the stable-dose period for the groups receiving fampridine 10 mg ($p=0.018$) and 15 mg ($p=0.003$) twice daily, but not for the group treated with 20 mg twice daily. There was no significant difference between treatment and placebo in any other secondary measure. Post hoc analysis identified “consistent responders” – patients who responded each time to treatment. There were significantly more “consistent responders” in the treatment groups than in the placebo group (36.7% compared with 8.5%) Adverse effects were generally mild to moderate and were seen at higher doses.

Limitations: The study was sponsored by Acorda Therapeutics, so there is an inherent possibility of bias. The authors report variability in change in T25FW in SEM, which underestimates true variability in the data. SD would have been a better measure of variability. Given the day-to-day variations experienced by people with MS, it may be difficult for a participant or a clinical observer to separate a treatment-related change from disease-related change unless there is a pattern of consistency over time. The authors state that “consistency of benefit may be a more selective measure of treatment effect than magnitude of change,” yet their primary measure is magnitude of change. That said, accounting for “consistent responders” makes the drug seem more efficacious than it really was.

Conclusion: The authors concluded that a subgroup of patients, when treated with fampridine, experiences a clinically relevant improvement in walking ability, which is sustained for at least

14 weeks. The authors slightly misrepresent the data – the average improvement in patients who responded to therapy was statistically significant but may not be clinically significant. Further studies looking at the long term (longer than 14 weeks) safety and efficacy of dalfampridine may be warranted.

Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, Marinucci LN, Blight AR; Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet. 2009 Feb 28;373(9665):732-8.⁶

Study Design: Randomized, double-blind, placebo-controlled, parallel trial

Description of Study:

Methods: Patients were randomized in a 2:1 ratio to receive 10 mg Fampridine SR BID or placebo BID. They returned for four visits over the course of the 14 weeks of double-blind treatment. The primary outcome was the proportion of patients with >20% improvement on the Timed-25 foot Walk (T25FW). Lower extremity manual muscle test (LEMMT) and the Ashworth Score for spasticity were secondary outcomes.

Outcome Results: The proportion of timed walk responders was higher in the fampridine group (78/224 or 35%) than in the placebo group (6/72 or 8%; $p < 0.0001$). In patients who responded to treatment, walking speed improved by 25.2% (95% CI 21.5% to 28.8%), compared to 4.7% (1.0% to 8.4%) in the placebo group. The average improvement in the LEMMT score for the fampridine-treated timed walk responders during the double-blind period was 0.18 compared with 0.04 for the placebo group ($p = 0.0002$). The difference in the Ashworth score was not statistically significantly different for the responders or the placebo group.

Limitations: The study was sponsored by Acorda Therapeutics, so there is an inherent possibility of bias. The authors determined clinical effectiveness of fampridine, irrespective of disease course type or concomitant treatment with immunomodulators; while the investigators did stratify patients by disease course type and concomitant treatment with immunomodulators, it does not appear that statistical analysis was performed.

Conclusion: The authors concluded that dalfampridine improved walking ability in some people with multiple sclerosis. They state that this improvement has a clinically meaningful therapeutic benefit, however, this is misleading. As in the previous study, the authors report what may or may not be clinically significant (by their inclusion criteria, 25.2% reduction in T25FW could be as little as 1.5 seconds) in only a small subset of the treatment sample. Reporting the data this way makes dalfampridine seem more useful than it may be. Possible research determining WHY some patients respond to dalfampridine while others do not could help to determine which patients would most benefit from its use.

Vollmer T, Henney HR 3rd. Pharmacokinetics and tolerability of single escalating doses of fampridine sustained-release tablets in patients with multiple sclerosis: a Phase I-II, open-label trial. Clin Ther. 2009 Oct;31(10):2206-14.⁷

Study Design: Phase I-II, open-label, crossover trial conducted at two sites

Description of Study:

Methods: 24 patients with MS received four doses of fampridine SR: 5 mg, 10 mg, 15 mg, and 20 mg with a four-day washout period between doses. Blood samples were drawn at baseline (0.5 hours before the dose), hourly for the first 8 hours, and then at 10, 12, 14, 18, and 24 hours, and pharmacokinetic parameters were evaluated. Patients were monitored on ECG at baseline and at 1, 4, 12, and 24 hours after each dose. In addition, patients were instructed to report any adverse events for 14 days after the conclusion of the study.

Outcome Results: The mean T_{max} for the various doses ranged from 3.36 to 3.92 hours, with an overall mean T_{max} of 3.75 hours (95% CI 3.52 – 3.98). The overall mean $t_{1/2}$ was 5.47 hours (95% CI 5.05–5.89). Both sex and weight affected the pharmacokinetic parameters of fampridine SR. 10 patients reported 11 adverse events. Dizziness was the most commonly reported AE (7 incidents reported by 6 patients [1 at 10 mg, 3 at 15 mg, and 3 at 20 mg]) followed by amblyopia, asthenia, headache, and ataxia, each with one report. Ten adverse events were rated mild to moderate; one report of dizziness was rated severe. No patients discontinued treatment due to adverse events.

Limitations: The study was supported by Acorda Therapeutics, the manufacturer of dalfampridine. The primary author has been a consultant for Acorda Therapeutics, and the secondary author is an employee of the company, so there is a potential conflict of interest. The study had a small sample size (n=24), so it may have been underpowered. As it was open-label, participants may have been more likely to report adverse effects at higher doses. Investigators, likewise, may have been biased in attributing adverse events to lower doses of the study drug as they were charged with determining the clinical relevance of any laboratory values outside normal ranges or ECG changes from baseline. The drug was administered in the fasting state, so pharmacokinetics could be different in the fed state. Finally, all participants were white, so potential pharmacogenomic differences between ethnic groups were not addressed.

Conclusion: The authors concluded that in these patients with MS, fampridine SR (5-20 mg) had a potentially advantageous pharmacokinetic profile relative to that associated with immediate-release fampridine and was generally well tolerated. Despite the study limitations, the authors' conclusions appear to be correct. Future randomized, placebo-controlled parallel trials looking at pharmacokinetics and safety in larger, more diverse samples are needed to extrapolate results to a broader population.

Contraindications^{1,2,3,4}:

History of Seizure Disorder: Seizures were noted with dalfampridine, and the seizure risk increases with increasing dalfampridine doses. Patients with a seizure history or with evidence of epileptiform activity on an EEG were excluded from trials. The seizure risk from dalfampridine in patients with epileptiform activity on EEG is unknown and may be substantially higher. If a seizure occurs, discontinue dalfampridine, and do not restart the drug.

Renal Failure: Cautious use of dalfampridine by anyone with renal disease is warranted, as dalfampridine is substantially excreted by the kidney, and the seizure risk is greater with increased drug exposure. The clearance of dalfampridine is significantly correlated with creatinine clearance.

Precautions^{1,2,3,4}:

Mild Renal Impairment (CrCl = 51-80 mL/min): The seizure risk is unknown for patients with a CrCl of 51—80 ml/min, but dalfampridine plasma concentrations may approach those observed at a dose of 15 mg twice daily, which is a dose that may be associated with an increased seizure risk. There is no specific dose adjustment recommended by the manufacturer.

Pregnancy: Dalfampridine is a FDA pregnancy category C drug. In animals, decreased offspring viability and growth at doses similar to the maximum recommended human dose of 10 mg PO every 12 hours were noted. As there are no adequate and well-controlled studies in pregnant women, the use of dalfampridine is only recommended if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation: Dalfampridine excretion into human milk is unknown. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Pediatric Use: The safety and efficacy of dalfampridine in children and adolescents have not been established.

Geriatric Use: Cautious use of dalfampridine in the elderly is warranted, as renal function declines with age. The manufacturer recommends that clinicians estimate the patient's creatinine clearance before and during dalfampridine receipt.

Adverse Effects³:

Occurring in >10% of patients

Genitourinary

Urinary tract infection (12%)

Occurring in >1% to <10% of patients

Central nervous system

- Insomnia (9%)
- Dizziness (7%)
- Headache (7%)
- Multiple sclerosis relapse (4%)
- Seizures (up to 4%; dose-dependent)

Gastrointestinal

- Nausea (7%)
- Constipation (3%)
- Dyspepsia (2%)

Neuromuscular & skeletal

- Weakness (7%)
- Back pain (5%)
- Balance disorder (5%)
- Paresthesia (4%)

Respiratory

- Nasopharyngitis (4%)
- Pharyngolaryngeal pain (2%)

Drug Interactions²:

Co-administration with other forms of 4-aminopyridine such as 4-AP or fampridine
The active ingredient is the same. There is potential for dose-related adverse reactions, like seizures.

Dosing/Administration^{1,2,3,4}:

Adult Dosing

Oral: 10 mg every 12 hours (maximum daily dose: 20 mg); no additional benefit seen with doses >20 mg/day. Tablets should be taken whole, not crushed, chewed, divided, or dissolved.

Pediatric Dosing

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

Geriatric Dosing

20 mg/day PO, administered as 10 mg every 12 hours.

Renal Impairment

Contraindicated in patients with creatinine clearance ≤ 50 mL/min. Caution is advised in patients with creatinine clearance 51-80 mL/min, but the manufacturer does not recommend a specific dose adjustment.

Hepatic Impairment

No dose adjustment necessary with hepatic impairment.

Concerns⁸:

Cost: Treatment with dalfampridine can cost as much as \$13,000 annually. Immediate release 4-AP can be obtained through compounding for as little as \$20 per month (\$0.35 for one 10 mg capsule.) While IR 4-AP would require tid or qid dosing, the cost of dalfampridine is 50-fold higher than 4-AP.

Conclusion:

While dalfampridine has shown some benefit in certain patient groups, its marginal efficacy, high cost, and potential safety concerns make it a poor choice for initial MS therapy. It is possible that modest outcomes seen in clinical trials may underestimate true gains in those patients who do respond to the drug. Until it is possible to determine which patients will respond to the drug, dalfampridine should not be recommended. Further study with concurrent MS treatment with other drugs could help to determine dalfampridine's place in therapy.

Recommended References:

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5. Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, Cohen R, Marinucci LN, Blight AR; Fampridine MS-F202 Study Group. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology*. 2008 Oct 7;71(15):1134-41.
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8. Hauser SL, Johnston SC. 4-aminopyridine: new life for an old drug. *Ann Neurol*. 2010 Jul;68(1):A8-9.

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