What is the medication?

Generic: dalfampridine

Brand name: AMPYRA

Has the medication received US Food and Drug Administration (FDA) approval?

Yes – 10-mg twice-daily dose approved on January 22, 2010.

If so, what are the indications and uses?

- Indicated to improve walking in patients with multiple sclerosis (MS), demonstrated by an increase in walking speed.
- Usage not restricted to any particular disease course or stage of MS.
- Safety and effectiveness in patients younger than 18 years of age have not been established.

What were the findings in the pivotal trials of this medication?

- Two phase III, randomized, placebo-controlled, double-blind clinical trials involving a combined total of 540 patients demonstrated improvement in walking. An initial walking speed between 8 and 45 seconds was required for inclusion. No patients with epilepsy or epileptiform activity on a screening EEG were admitted. Patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min) were excluded from Trial 2.
- Patients with MS for an average duration of 13 years and a mean Expanded Disability Status Scale (EDSS) score of 6.0 were treated for 14 weeks in Trial 1 and 9 weeks in Trial 2. Walking speed for 25 feet was assessed before, during, and after treatment.
- The primary outcome measure utilized a responder analysis of timed 25-foot walk (T25FW) data. To be considered a responder, 3 of 4 walking times during treatment had to be faster than the fastest walking time off treatment. A significantly greater proportion of patients taking dalfampridine as compared with patients taking placebo were responders in both Trial 1 (34.8% vs. 8.3%) and Trial 2 (42.9% vs. 9.3%).
Trial 1 (MS-F203) (Goodman AD et al., Lancet 2009; 373(9665): 732–8)

- **Trial design:** Eligible patients were 18–70 years of age (youngest enrolled patient was 24) with clinically definite MS of any type or duration and the ability to complete two trials of the T25FW in an average time of 8–45 seconds. Patients were excluded if they had an MS exacerbation within 60 days of screening, a history of seizures, or any condition that would interfere with the study protocol. The 301 participants were tested with a T25FW at screening and during a single-blind, placebo run-in arm, 1, 2, and 3 weeks later, at which time they were randomized to either active treatment with dalfampridine 10 mg every 12 hours (n=229) or placebo (n=72) for 14 weeks. The T25FW was performed after 2, 6, 10, and 14 weeks of therapy. At the end of the 14-week double-blind treatment period, patients began a 4-week period of no treatment, with assessment of the T25FW at 2 and 4 weeks following treatment cessation.

- **Primary endpoint:** The primary outcome was the proportion of responders, determined on the basis of the average T25FW for each visit. The T25FW was done twice at each visit, allowing a maximum of 5 minutes between measurements. The times of the two walks were averaged to derive a value for that visit. A responder was defined as having an average walk speed on three or four assessments during treatment that was faster than his or her fastest walk speed without dalfampridine.

- **Secondary endpoints:**
  - Ashworth Scale score for spasticity
  - Lower Extremity Manual Muscle Test (LEMMT)
  - Twelve-item Multiple Sclerosis Walking Scale-12 (MSWS-12)
  - Clinical Global Impressions (CGI) and Subject Global Assessment (SGA) scale scores

- **Results:**
  - Proportion of responders was significantly higher for the dalfampridine group (78/224 or 34.8%) than for the placebo group (6/72 or 8.3%), \( \rho < 0.0001 \). Percent improvement in walking speed in responders treated with dalfampridine averaged 25.2% as compared to 4.7% in all participants treated with placebo.
The group treated with dalfampridine showed a greater improvement than the group treated with placebo in average change from baseline in walking speed (nominal \( p = 0.0004 \)), LEMMT score (nominal \( \rho = 0.0029 \)), and Ashworth score (nominal \( \rho = 0.0210 \)).

Responders treated with dalfampridine showed greater improvement on the MSWS-12 (-6.84) than nonresponders treated with dalfampridine (+0.05).

Safety data were consistent with data from previous studies.

Global impression scores (CGI and SGA) were significantly more positive for responders as compared with nonresponders, irrespective of treatment.


- **Trial design:** This trial was similar in overall design to Trial 1, with several specific differences.

  - Two hundred thirty-nine subjects were randomized in a 1:1 ratio (dalfampridine \( n = 120 \); placebo \( n = 119 \)).

  - T25FW was evaluated in double-blind treatment over 9 weeks, with four on-treatment visits at 2-week intervals.

  - An additional double-blind treatment visit was added to collect data from the end of the 12-hour dosing schedule. This measurement determined whether the treatment effect was maintained over the full between-dose interval.

- **Results:** Highly consistent with those from Trial 1.

  - Responders were more common in the group treated with dalfampridine (42.9%) than in the group treated with placebo (9.3%), \( \rho < 0.001 \).

  - Consistent improvements in walking speed were associated with improvement in MSWS-12 scores.

  - Treatment effect with dalfampridine was maintained through the 12-hour treatment interval.

- **Extension data:** Average improvement in walking speed over baseline gradually decreased over 2 years of treatment, but improvement was still evident at the last visit (approximately 2.5 years from the original baseline).
What is the mechanism of action and the rationale for its use in MS?

- The exact mechanism of action for the effect of dalfampridine on walking is unknown.

- Current thinking is that dalfampridine improves conduction of action potentials along the axon by blocking the efflux of potassium ions from axons along demyelinated areas, thus prolonging depolarization and/or preventing shifts in potassium concentration that could lead to impaired repolarization of the axonal membrane.

- It is hypothesized that improved transmission of neural impulses occurs in multiple impaired axons, leading to better modulation of important complex motor acts such as walking.

What is the delivery route and recommended dosing?

- 10-mg taken orally approximately 12 hours apart, with or without food.

- The tablet should not be broken or crushed.

Can this medication be used with other medications?

- Dalfampridine should not be taken with other forms of 4-aminopyridine (4-AP, fampridine) since the active ingredient in all of these products is the same. Patients should discontinue taking any product containing 4-aminopyridine prior to starting dalfampridine.

- No significant interactions between dalfampridine and other medications have been identified; in particular, no pharmacokinetic drug-drug interaction was observed with coadministration of dalfampridine 15-mg and baclofen 10-mg.

- Dalfampridine can be taken concurrently with disease-modifying therapies (DMTs) for MS.

How does the expected treatment effect compare with the treatment effect provided by other available medications?

- 4-aminopyridine is the only available medication that has the same mechanism of action as dalfampridine. Although 4-AP can be dispensed by compounding pharmacies, and the active ingredient in the two medications is the same, 4-AP is not FDA-approved and should not be considered an alternative to dalfampridine. Dalfampridine is a sustained-release preparation that results in more predictable blood levels.

- Antispasticity agents such as baclofen, tizanidine, and benzodiazepines may also improve walking ability in MS, but these agents have not been compared directly with dalfampridine in a controlled clinical trial.
What are the possible short-term side effects? What is the range of severity of side effects, and what are the recommended management strategies?

- A dose-dependent increase in the incidence of seizures has been observed in controlled and open-label trials of dalfampridine. For the 10-mg twice-daily dosing in open-label extension trials in MS patients, the incidence of seizure was 0.41 per 100 person-years. Dalfampridine is contraindicated in individuals with a history of seizures and should be discontinued and not resumed if a seizure occurs while a person is taking dalfampridine. The risk of seizures in patients with epileptiform activity on EEG is unknown, as these patients were excluded from the dalfampridine clinical trials.

- The most common side effects in MS clinical trials, including insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, paresthesias, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain, would be expected to resolve with discontinuation of treatment. Paresthesias resulting from dalfampridine often become less bothersome with time on the medication.

- MS relapses were reported more frequently in MS patients on dalfampridine (4%) as compared with patients on placebo (3%) (most likely due to chance – See author commentary).

- In controlled studies in MS patients, urinary tract infections were reported more frequently as adverse reactions in patients receiving dalfampridine 10 mg twice daily (12%) than in those receiving placebo (8%) (most likely due to chance – See author commentary).

What are the known long-range (morbidity and mortality) health risks?

- There are no known long-range health risks with dalfampridine.

- In an individual taking dalfampridine who develops unrecognized renal impairment, toxicities, including seizures, could result due to elevated blood levels of the medication.

Has the FDA included any black box warnings about this medication?

The FDA has not included any black box warnings about dalfampridine.

What training is recommended or required for clinicians or patients before initiating this treatment?

No specific training is required for clinicians or patients.
What is the pregnancy rating for this medication, and what is known about possible carcinogenesis, mutagenesis, and impairment of fertility?

- Dalfampridine is Pregnancy Category C; animal data suggest it may cause fetal harm.
- Dalfampridine should not be taken by women who are breastfeeding.
- Dalfampridine has no known effects on carcinogenesis, mutagenesis, or fertility.

Does this medication interact or interfere with oral contraceptives?

Dalfampridine is not known to interact or interfere with oral contraceptives.

Has the FDA recommended or required a safety-monitoring program?

The FDA has not recommended or required a safety-monitoring program. The Risk Evaluation and Mitigation Strategy (REMS) program is limited to disseminating the change in the generic name and potential seizure risk.

What kind of safety monitoring is recommended (including prescreening, routine check-ups, and laboratory tests)?

- Dalfampridine should not be used in patients with a history of seizure disorder; it has not been evaluated in patients with a history of seizures or with evidence of epileptiform activity on EEG (See author commentary).
- Dalfampridine should not be used in patients with moderate or severe kidney impairment. It is eliminated through the kidneys as an unchanged medication; because patients with renal impairment would require a dose lower than 10 mg twice daily and no strength under 10 mg is available, it is contraindicated in patients with moderate or severe renal impairment.
- Clinical studies of dalfampridine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Because older patients are more likely to have decreased renal function, it is particularly important to know the estimated creatinine clearance in these patients.

Are there any recommended limits on duration of treatment with this medication?

There are no recommended limits on duration of treatment with this medication.
What happens following termination of treatment with this medication?

Dalfampridine may be discontinued at any time. Any symptomatic benefits of the medication will abate over the following 24 hours.

- **What treatment options are available for patients who have been treated with dalfampridine?**

  Currently there are no other FDA-approved medications to improve walking in patients with MS. Patients may benefit from utilization of antispasticity medications, assistive devices, or physical and occupational therapy to improve walking.

- **What is the washout period?**

  Elimination of dalfampridine and its metabolites is nearly complete after 24 hours. The elimination half-life of dalfampridine following administration of the extended-release tablet is 5.2 to 6.5 hours. The plasma half-life of the sulfate conjugate is approximately 7.6 hours.

How can a provider identify a suboptimal treatment response?

Patients who do not show an improvement in walking could be considered suboptimal responders. Improvement in walking is usually evident within 2 to 4 weeks of starting dalfampridine.

Is the manufacturer/distributor offering any financial assistance program for patients?

- When dalfampridine is prescribed, AMPYRA Patient Support Services (APSS) will confirm insurance and eligibility for the copay program.

  - □ For people who are eligible – and where allowed by law – those with private insurance may pay no more than $40 per month for their prescriptions.

  - □ If the patient cannot afford the cost, the patient assistance team will determine whether the person is eligible to receive dalfampridine at no cost.

  - □ The most up-to-date information about APSS can be obtained by calling 1-888-881-1918.

- Dalfampridine coverage varies by Medicare Part D plan. Medicare Part D beneficiaries are not eligible to participate in the Acorda copay program; Medicare Part D beneficiaries who qualify for the Acorda Patient Assistance Program, regardless
of whether they have reached the “doughnut hole” (coverage gap), may receive dalfampridine at no charge for the remainder of the year.

- Medicaid coverage for dalfampridine varies by state.

**Are there any special considerations with this medication?**

Dalfampridine can be used by patients with any clinical MS type (relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing).

**COMMENTARY BY AUTHORS**

- Although a slight increase in MS relapses was reported with dalfampridine (4%) as compared with placebo (3%) at the doses tested in the two phase III clinical trials, the magnitude of difference is most likely due to chance.

- Although a slight increase in urinary tract infections was reported with dalfampridine (12%) as compared with placebo (8%) in the controlled clinical trials, this may have been due to chance.

- There is no formal requirement for monitoring of renal function during treatment with dalfampridine other than an initial determination of renal function prior to initiation of treatment. Periodic monitoring of renal function during treatment should be considered if there are clinical circumstances in which renal function might reasonably be altered.

- Evidence is lacking regarding the utility of routinely obtaining an EEG prior to initiating treatment with dalfampridine. A clinical history of seizures is a contraindication to treatment with dalfampridine, and there may be clinical circumstances where a provider chooses to obtain an EEG prior to initiating treatment with dalfampridine.

- Outside of the setting of large randomized controlled trials, there are reported benefit of dalfampridine on aspects of MS other than walking, such as improved cognition, fatigue, arm function, and vision. Although providers may choose to prescribe dalfampridine for these non–FDA-approved indications, data are lacking concerning the safety and efficacy of such uses, and the cost may not be covered by insurance carriers.

- It is appropriate to discontinue treatment if there is no objective improvement after 3-6 weeks on dalfampridine.
WEB LINKS PROVIDED IN THIS DOCUMENT


AUTHORS:
Michael Kaufman, MD, Amy Perrin-Ross, APN, MSN, CNRN, MSCN, Ruth Whitham, MD

EDITOR:
Rosalind Kalb, PhD

DISCLAIMER:
The Emerging Therapies Collaborative is proud to be a source of information about multiple sclerosis. Our comments are based on published data and expert opinion, but do not represent individual therapeutic recommendations or prescriptions. For specific information and advice, consult your physician.

FOR DISCLOSURES AND OTHER INFORMATION:
Please visit our website at http://www.ms-coalition.org/emergingtherapies or email us at emergingtherapies@ms-coalition.org.

For additional information, healthcare professionals are invited to email the National MS Society’s Professional Resource Center at healthprof_info@nmss.org.
On July 23, 2012, the Food and Drug Administration (FDA) issued a safety update regarding the risk of seizures in patients taking dalfampridine (Ampyra), noting that seizures are a known risk of dalfampridine therapy and that the majority of seizures reported in postmarketing surveillance occurred within days to weeks of starting the drug in patients with no prior history of seizures.

The FDA is updating the drug label to clarify recommendations that kidney function (creatinine clearance) should be checked prior to initiation of dalfampridine treatment in all patients and should be monitored at least annually in all patients taking the drug.

The safety update notes the following:

• Dalfampridine is contraindicated in patients with a history of seizures or with moderate to severe renal impairment (CrCl <50 mL/min).
• Mild renal impairment is common after the age of 50 years.
• The potential benefits of dalfampridine treatment should be carefully considered against the risk of seizures before use of dalfampridine in patients with mild renal impairment (CrCl 51–80 mL/min).
• Most of the seizures reported with dalfampridine treatment occurred in patients with no history of seizures.
• A patient’s CrCl (calculated using the Cockcroft-Gault equation):

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

• Renal function should be monitored at least annually while dalfampridine treatment continues, even when serum creatinine levels appear to be normal.
• The maximum recommended dose of dalfampridine is 10 mg twice daily (taken 12 hours apart). The tablets should be taken whole and not divided, crushed, chewed or dissolved.
• Patients should be reminded not to take double or extra doses if a dose is missed. Adverse effects, including seizures, are more frequent at higher doses.
• Dalfampridine should be discontinued permanently if a seizure occurs.

DISCLAIMER:
The Emerging Therapies Collaborative is proud to be a source of information about multiple sclerosis. Our comments are based on published data and expert opinion, but do not represent individual therapeutic recommendations or prescriptions. For specific information and advice, consult your physician.