Mellen Center Approaches: Use of dalfampridine (Amrya).

Q: What is dalfampridine and for what is it approved?

A: Dalfampridine (Amrya) was FDA approved January 22nd, 2010 as an oral medication to improve walking in patients with MS. Dalfampridine is a symptomatic therapy, and can be used in combination with disease modifying agents. It is an extended release form of 4-aminopyridine (previously known as fampridine).

Dalfampridine is a broad-spectrum inhibitor of voltage-sensitive potassium channels. In laboratory studies Dalfampridine has been found to improve impulse conduction in demyelinated nerve fibers and to increase synaptic transmitter release at nerve endings. (Judge, 2006).

Dalfampridine is administered as a 10 mg timed release pill every twelve hours. In two phase III trials in patients with MS randomized to dalfampridine vs. placebo, a significantly greater percentage of patients were ‘responders’ on dalfampridine than on placebo (Goodman et al, 2008; Goodman et al 2009).

A responder was defined as a patient who showed faster walking speed while on therapy than while not on therapy. About 1/3 patients responded to dalfampridine in these studies (Goodman et al, 2009). The increased response rate in the dalfampridine group was observed across all four major types of MS (relapsing remitting, secondary progressive, progressive relapsing and primary progressive).

Q: Who should be considered for dalfampridine?

A: Reasonable candidates to try dalfampridine are patients with any type of MS who have walking problems from MS and for whom a modest improvement in walking would be of clinical benefit. Other functions might improve (for example visual acuity, diplopia), but this was not demonstrated in the pivotal trials. Dalfampridine is not expected to restore ambulation in MS patients who are wheelchair-bound.

We note that the magnitude of effect of dalfampridine is modest. We would not expect patients to change the type of assistive device that they use (that is, if they are using a Rollator, we would not expect them to switch to a cane or no device due to dalfampridine). The average increase in walking speed reported in the clinical trials was around 25%.

Q: Are there any types of gait disturbance for which dalfampridine is not indicated?

Mellen Center Approaches, Amrya use in MS. Version 1 Feb 2010 Page 1 of 4
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Cleveland Clinic Mellen Center for Multiple Sclerosis

A: Ampyra was demonstrated to improve walking speed on the Timed-25 Foot Walk. There was also improvement of scores on the MS-Walking Scale 12, a patient-reported measure of walking performance in daily activities. There is no formal limitation for dalfampridine use regarding the specific type of gait abnormality, but we expect it will be more beneficial in patients with spastic weakness over those with mostly cerebellar or sensory ataxia. It is essential to remember that dalfampridine does not address all gait problems. For example, dalfampridine does not improve gait stability or need for assistive device and/or physical therapy, so we recommend these be addressed first, since prescribing a medication that increases walking speed in a patient with unsafe gait may lead to increased risk of falling.

Q: How is dalfampridine dosed?

A: There is one dosage, 10 mg tablet twice a day, taken with or without food. Doses should be approximately 12 hours apart. PATIENTS SHOULD NOT DOUBLE UP DOSES IF THEY MISS A DOSE to reduce the risk of side-effects, including seizures. There was no additional benefit above this dose in clinical trials, and side effects including seizures were more common at higher doses. Tablets should be taken whole, not crushed or chewed.

There is no data on use in pediatric age groups and this medicine is therefore not recommended at present for patients younger than 18 years of age. This medicine should not be used by women who are pregnant or nursing. Based on animal data, this medicine may cause fetal harm. Geriatric patients are at higher risk of renal dysfunction, and it is important to know creatinine clearance in this population as more than 90% of the medicine is excreted unchanged in the urine.

Q: When would you expect to see an effect from dalfampridine?

A: We would expect to see a response within 2-4 weeks. This is a medication which should have its maximal effectively rapidly and thus prolonged trials of this medicine beyond a month are not helpful.

Q: What are the risks of dalfampridine and what can be done to reduce those risks?

A: The FDA approved dalfampridine with a risk evaluation and mitigation strategy (REMS) program comprising a medication guide and communication plan. The goals of the communication plan are to inform patients about the serious risks, including seizures (which are associated with use of higher than recommended doses of dalfampridine therapy) and the change of the established name from fampridine to dalfampridine.

Detailed information about prescribing dalfampridine is available from the following website:

http://www.ampyra.com/hcp/

Mellen Center Approaches, Ampyra use in MS. Version 1 Feb 2010 Page 2 of 4
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Dalfampridine is contraindicated in patients who have previously had seizures, and may cause seizures de novo, particularly at higher than recommended doses. It is also contraindicated in patients with moderate to severe renal impairment (creatinine clearance \( \leq \) 50 mL/min). Other reported side effects seen at \( \geq 2\% \) of dalfampridine-treated patients in treatment trials included the following: urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

Dalfampridine should not be used along with other forms of 4-aminopyridine. For example, patients who are currently on compounded 4-AP must stop the compounded medication before starting dalfampridine.

**Q: What about doing an EEG prior to beginning dalfampridine?**

A: A history of prior seizures is a contraindication for beginning Ampyra. All participants in the licensing clinical trials for dalfampridine received screening EEGs and were excluded if there was evidence for epileptiform activity on that screening EEG. Therefore, there is no published experience of dalfampridine in patients with epileptiform activity on screening EEG. We are at present recommending an EEG prior to beginning dalfampridine as a screen for markers of a seizure predisposition. If there are epileptiform changes on EEG, we would consider not using dalfampridine. The relevance of other, nonspecific EEG changes to the risk of seizures related to dalfampridine are not known. However we would not look at nonspecific EEG changes as a contraindication to using dalfampridine at this time.

**Q: What is the process to prescribe dalfampridine?**

A: Information on prescribing dalfampridine can be obtained at the following website:

http://www.ampyra.com/hcp/

Dalfampridine is presently available only through a specialty pharmacy. Specific forms need to be submitted with insurance information for dalfampridine approval.

**Q: What else should I consider when prescribing dalfampridine?**

A: Walking is a complex neurobiological function and there are many ways that we can improve walking skills beyond the use of dalfampridine. We think that patients should be assessed by a physical therapist skilled at gait assessment. PT exercises aimed at balance and strength, provision of walking aides (Cane, Canadian crutches, walker, Rollator, etc.) and/or bracing (for example ankle splinting, etc.) may significantly improve gait efficiency and safety. When prescribing dalfampridine we recommend a comprehensive approach to walking.

Mellen Center Approaches, Ampyra use in MS. Version 1 Feb 2010 Page 3 of 4
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Cleveland Clinic Mellen Center for Multiple Sclerosis

References:


