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Month/Year of Review: July 2013
Generic Name: Dalfampridine
Brand Name: (Manufacturer): Ampyra™
Class: Potassium Channel Blocker for MS symptoms

End date of literature search: June 2013
Manufacturer: Acorda Therapeutics, Inc
Dossier received: Yes
Comparator Therapies: None

FDA Approved Indications:[1]
Dalfampridine extended release tablets are indicated for the improvement of walking in patients with multiple sclerosis (MS), as demonstrated by increased walking speed.

Conclusions:

1. **Does FAM produce changes in disability or impairment scales assessing motor function?**
   The differences between FAM-treated and placebo-treated patients for change in walking speed and MSWS-12 were small and achieved inconsistent statistical significance.

   In the phase 2 trial, there was no statistically significant difference between FAM-treated and placebo-treated patients for mean percent change in walking speed as assessed by the T25FW. Therefore, post-hoc data analysis was performed to identify a new endpoint—response to treatment—that would achieve statistical significance in the phase 3 trials. Statistical significance was indeed achieved for the primary endpoint in the two phase 3 clinical trials. However, FDA analysis shows the absolute difference in walking speed between responders and non-responder is about 2 seconds over 25 feet. No published information is available for distances beyond 25 feet. A post approval subgroup analysis assessed the effect in distances longer than 25 feet which showed a significant improvement; however this analysis has not been published.

   Other limitations of the studies include lack of long-term data and lack of clarity on how one would determine in practice who could potentially respond to FAM. Three unpublished extension studies have been completed that address the long-term efficacy and safety of FAM; however, no studies have been published addressing quality of life or activities of daily living. MS has no cure; therefore, the mainstays of treatment are disease-modifying agents that slow the progression of the disease and symptomatic and supportive therapies. FAM is a potassium channel inhibitor that may act by increasing action potential conduction in demyelinated axons, thereby improving walking speed

2. **Does FAM change disease progression, hospitalization rates, improve the performance of activities of daily living, or reduce resources used for home care?**
   FAM is not a disease-modifying agent and, therefore, does not reduce relapse rates or slow disease progression. No studies have been performed addressing whether the use of FAM decreases hospitalization rates, reduces resources used for home care, or improves the performance of activities of daily living.

3. **Does FAM improve quality of life?**
   Quality of life was not measured in the phase 3 studies. The phase 2 study reported the MSQLI was used as a secondary efficacy measure but did not report the results, thus there is no evidence FAM improves quality of life.

4. **How does FAM compare with non-pharmacologic therapies, such as exercise therapy?**
   No head-to-head comparisons have been performed between FAM and exercise therapy or any other therapy. While exercise is recommended for those with MS, there is little consistent data concerning its efficacy in improving walking in MS.[2]

5. **Is FAM safe?**

The most concerning adverse event for FAM-treated patients is the risk of seizures. Doses exceeding 10 mg twice daily have been associated with increased seizure risk. Also, seizure risk has not been truly evaluated in studies of FAM, because patients with a history of seizure and evidence of epileptiform activity on EEG have been excluded and safety evaluations have been performed in just 807 MS patients taking FAM SR. A postmarketing analysis demonstrated that during the first year, a total of 85 cases of seizure were reported (5.4 cases per 1000 patient-years).[3]

Ampyra does have a Risk Evaluation and Mitigation Strategy (REMS), including a medication guide and annual letters to prescribers and pharmacists with warnings about the potential risk of seizure. Extension trials that may shed more light on safety have yet to be published.

Other noteworthy adverse events are the rate of UTIs (NNH 25) and the rates of dizziness (NNH 33), asthenia (NNH 33), weakness (NNH 33), and balance disorder (NNH25) in patients who are having difficulty with mobility. Nevertheless, the overall discontinuation rate due to adverse events for FAM-treated patients was just 4% compared with 2% for placebo-treated patients.

No evidence of mutagenicity, carcinogenicity, or impaired fertility has been observed in animals given doses well above the MRHD. However, decreased offspring viability and growth has been observed in animals given doses similar to the MRHD. Therefore, managing the risks and benefits of using FAM in pregnancy is real, especially given that MS is a chronic disease that disproportionately affects women.

6. **Is the benefit of FAM commensurate with the cost?**
   Because FAM is the only approved drug for the indication improvement in walking in MS patients, one cannot compare its cost to other drugs. One could ask whether the improvement in walking leads to direct or indirect healthcare cost savings, but no pharmacoeconomic studies have been performed for FAM.

Recommendations:

- Consider adding to the PA criteria that physician reassessment after a 12-week trial includes demonstration of a ≥20% improvement in walking speed as assessed by the T25FW (Appendix 1).
- Recommend revising PA criteria to allow for use in patients with moderate ambulatory dysfunction who do not require a walking aid.
- Recommend to consider dalfampridine for the high cost marginal benefit policy.

BACKGROUND/CURRENT LANDSCAPE

FAM is the first drug approved for the improvement of walking in MS patients, and the measure of efficacy used in the two pivotal FAM phase 3 trials on which FAM's approval has been based is a novel one. Because MS has no cure, disease modifying agents and symptomatic therapies are the mainstay for managing the disease.

MS is a chronic, progressive, immune-mediated disorder characterized by inflammation of the white and gray matter of the central nervous system and destruction of axonal myelin sheaths, resulting in neurodegeneration and gliotic sclerosis. MS affects about 350,000 people in the US and more than 1 million worldwide. MS occurs 2 to 2.5 times more frequently in women than in men.[4,5]

Symptoms of MS typically present between the ages of 18 and 45 and include combinations of the following: fatigue; heat sensitivity; weakness; depression; bladder, bowel, or sexual dysfunction; or impaired vision, sensation, coordination or balance.[3, 4] Nearly 50 percent of those with MS will require the use of a walking aid within 15 to 25 years of diagnosis.[6]

The three major subtypes of MS are relapsing remitting, secondary progressive, and primary progressive. About 85 to 90 percent of patients present with relapsing remitting MS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with relapsing remitting MS develop secondary progressive MS within twenty to forty years, which is characterized by steady neurological decline with few or no clinically recognized relapses. About 10 to 15 percent of patients present with primary progressive MS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[34,5]

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The course of MS is highly unpredictable and varies from person to person. About 10 percent of patients have a relatively benign course and do well for more than 20 years, while about 70 percent develop secondary progression. Life expectancy may be slightly shorter for those with MS. In rare cases, patients with fulminant MS die within months of disease onset.[7]

The total mean annual cost of MS in 2004, which is after the introduction of disease modifying agents, has been estimated to be about $47,000 per patient.[8] Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).[9]

MS is managed by disease-modifying agents and symptomatic and supportive therapies. First-line disease-modifying agents for slowing the progression of MS and reducing the associated disability include interferon (IFN)-β1b (Betaseron), IFN-β1a (Avonex), IFN-β1a (Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone).[4,5] Many agents are used to treat the symptoms of MS, such as baclofen or tizanidine for spasticity and gabapentin or amitriptyline for neuropathy. Non-pharmacologic therapies for MS symptoms include physical therapy for spasticity, gait dysfunction, and imbalance as well as exercise for osteoporosis and walking mobility.[5-7] Now FAM has been approved for the improvement of walking.

In clinical trials of disease modifying agents, the most often used primary efficacy endpoint has been relapse rate, while disease progression as measured by change in Expanded Disability Status Scale (EDSS) score has been more often used as a secondary efficacy endpoint. The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored from 0, no neurological abnormality, to 10, death from multiple sclerosis.[10-12] An EDSS of 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.[13]

In most clinical trials of disease modifying agents, progression has been defined as a sustained 3- or 6-month increase in EDSS of at least one point recorded in a period when the patient had no exacerbation. From the pooled data of three trials, the calculated relative risk of progression at 2 years for MS patients taking beta-interferon versus placebo was 0.70 (0.55–0.88, p=0.002).[10]

The measure of efficacy used in the two pivotal FAM phase 3 trials is a novel one that appears to have been created for the purpose of achieving clinical significance. The primary efficacy measure, called response to treatment, is defined as a consistent improvement in walking speed as measured by the Timed 25-Foot Walk (T25FW). The T25FW is a timed test of walking that measures patients' ability to safely and quickly walk 25 feet in his or her usual manner.[14] Four feet per second is normal walking speed. [15] A 20% change from baseline has been previously suggested to be a minimally clinical important difference.[16]

The T25FW is a component of the MS Functional Composite (MSFC), which was developed in the mid-1990s by the Clinical Outcomes Assessment Task Force of the National MS Society to overcome the limitations of the EDSS.[11, 15, 17] The MSFC, which was a secondary efficacy measure in a pivotal phase 2 FAM trial, is a composite measure of impairment and disability and, in addition to the T25FW, measures two other clinical dimensions: (1) the 9-Hole Peg Test (9HPT), which tests arm function and (2) the Paced Auditory Serial-Addition Task (PASAT), a cognitive function test.[17]

In FAM phase 3 trials, the 12-item MS walking scale (MSWS-12) was used to validate the clinical significance of the primary efficacy endpoint.[43] The MSWS-12 assesses MS patients' perspectives on their ambulatory disability. Patients rate the degree of limitation they've experienced in walking due to MS in the previous 2 weeks for each of 12 walking-related items. The ratings are summed and turned into a scale of 0 to 100, with higher scores indicating greater limitation on walking abilities.[19]

Efficacy:

Sustained-release FAM was approved by the FDA for improvement of walking in patient with MS based on two pivotal phase 3 clinical trials: MS-F203 and MS-F204.[13, 21] Both have been published. The phase 2 trial, MS-F202, also provides evidence concerning the efficacy of FAM and the origins of the primary endpoint used in the phase 3 trials.[20] (See Clinical Efficacy Evidence Table)

Low level evidence from two phase 3 studies and one phase 2 study show dalfampridine (FAM) statistically increases walking speed in a subset of patients with MS called timed-walk responders (TWRs). However, FDA analysis of the absolute difference in walking speed over 25 feet between responders and non-responders is small.

The phase 2 study MS-F202 was negative and compared three doses of sustained-release FAM with placebo in MS patients. The primary endpoint was mean percent change in walking speed during treatment using the Timed 25-Foot Walk (T25FW), which measures patients' ability to safely and quickly walk 25 feet and has been validated in MS.

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Though statistical significance for the endpoint was not achieved, researchers performed a post-hoc analysis that found a greater percentage of FAM-treated patients had a "consistent" improvement in walking speed. This newly created, as-yet-to-be-validated endpoint was called "response to treatment," and responders were defined as those whose walking speed for at least three visits during the double-blind treatment period of the trial was faster than the maximum speed in five non-treatment visits, four before and one after treatment.[18] The response rate for patients treated with FAM 10, 15, and 20 mg was 35.3%, 36.0%, and 38.6% and for placebo 8.5% (p value not given), giving an NNT of 3.55 (95% CI 2.16–4.94).[18] Therefore, response to treatment was used as the primary endpoint for the phase 3 trials

Published phase 3 study MS-F203 randomized 301 patients 3:1 to receive FAM 10 mg bid or placebo, respectively, during a 14-week, double-blind treatment period. Enrolled in the study were patients 18–70 years old with clinically defined MS who were able to complete two trials of the T25FW in an average time of 8–45 s at screening. The study population had an average EDSS of 5.8.[13] The range for the placebo population was 1.5–7.0 in one study; however, the mean ± SD was 5.6 ± 1.2 for the placebo group and the mean ± SD and range for the treatment groups, overall, were 5.8 ± 2.0 (2.5–6.5).[14] Similarly, in the second study, they were 5.8 ± 1.1 (2.5–6.5) for placebo and 5.0 ± 1.0 (2.5–7.0) for the treatment groups combined. Patients with EDSS scores between 4.5 and 6.5 have moderate ambulatory dysfunction. The cutoff 4.5 distinguishes patients with moderate dysfunction from patients with mild dysfunction. EDSS ≤ 6.5 are patients who have preservation of some ambulatory function.[21]

Patients who were unable to complete the T25FW within 45 s were excluded from the trial, implying that FAM lacks benefit in more severely disabled patients. This was corroborated by the FDA report in which reviewers said "the sponsor in 2005 alluded to the lack of reliability of the data in more disabled subjects when walking speed exceeded 45 second."[14]

Study MS-F203 found that, for a group of MS patients able to complete the T25FW within 45 s, the percentage of time walked responders (TWR) in the FAM group was 35% compared with 8% in the placebo group ($p<0.001$, OR 4.75; 95% CI 2.08–10.86), giving an NNT of 4.[13]

The phase 3 study MS-F204 was similar to that of MS-F203, except the double-blind treatment period was 9 weeks long. The investigators did not reveal why the lengths of the treatment phases of the two studies were different. The study found that the percentage of responders in the FAM group was 43% compared with 9% in the placebo ($p<0.001$), giving an NNT of 3.[19]

Though the phase 3 studies showed statistical significance for their primary endpoint, questions about the clinical significance of the endpoint remained, given that the endpoint has not yet been shown to be a valid one for assessing FAM or any other MS drug. The studies addressed this by asking patients to complete the MSWS-12 (a validated patient-based measure of the impact of MS on walking) and calculating the average change from baseline in the score. Researchers found a statistically significant decrease in MSWS-12 score for responders compared to non-responders, independent of treatment group: –6.84 (–9.65 to –4.02) versus 0.05 (–1.48 to 1.57), respectively, ($p=0.002$) for study MS-F203 and –6.04 (–9.75 to –2.52) versus 0.85 (–0.72 to 2.43).[13, 19]

The positive findings for the change in MSWS-12 are questionable. The MSWS-12 may be an inappropriate instrument to use to validate the results of the T25FW. Also, the analysis using the MSWS-12 should have been performed on the intent-to-treat population rather than responders versus non-responders. Therefore, the achieved change in MSWS-12 may not truly represent clinical significance.[14]

Investigators also performed an assessment of average change from baseline in walking speed for the responders versus placebo group. The changes in walking speed for FAM responders compared with total placebo group in study MS-F203 were 0.51 feet/s (0.41 to 0.61) and 0.1 feet/s (0.03 to 0.17), respectively.[13] FDA analysis of MS-F203 showed that this translated to a 1.75 s difference in walking speed between total non-responders and responders, a 1.99 s difference between placebo-treated responders and non-responders, and a 1.6 s difference between FAM-treated responders and non-responders.[14] The changes in walking speed for FAM responders versus total placebo group in study MS-F204 were 0.51 ft/s (0.43 to 0.59) versus 0.17 ft/s (0.10 to 0.23) for placebo group.[19] FDA analysis of MS-F204 showed that this translated to a 1.71 s difference in walking speed over 25 feet between total non-responders and responders, a 1.54 s difference between placebo-treated responders and non-responders, and a 2.15 s difference between FAM-treated responders and non-responders.[14]

Before FAM should be considered an option for improving the lives of MS patients, longer-term studies should be performed with more clinically relevant outcomes that include the impact FAM would have on the quality of life of MS patients or their activities of daily living, health, or homecare requirements. The phase 2 study included the Multiple

Sclerosis Quality of Life Inventory (MSQLI) as a secondary efficacy measure but the scores were not reported.[18] Extension studies (MS-F202 EXT, MS-F203 EXT, MS-F204 EXT), which have been completed but not yet published, may shed light on the long-term efficacy of FAM, but primarily in terms of walking speed.

Finally, assuming FAM allows patients to achieve clinically meaningful changes in mobility, it is unclear how one would use FAM in practice given that only a subset of patients are responders and no method is available to identify which patients would potentially respond. Patients should discontinue treatment after a 4 to 6 week trial of the drug if they are not responding.

FAM may have negligible benefit relative to its annual cost and its associated safety risks. Should criteria be developed to restrict FAM's use, the following should be included: FAM should be limited to those who (1) have moderate ambulatory dysfunction who do not require a walking aid or those that require the use of a walking aid, (2) be able to complete the T25FW in 8–45 s, and (3) do not have moderate or severe renal impairment or a history of seizure disorder or epileptiform activity on EEG. Physician reassessment by T25FW should be required after a 12-week trial and could include demonstration of a >20% improvement in walking speed as assessed by the T25W based on the suggested minimally clinically important difference.

Safety: In clinical trials, the most common serious adverse events occurring in FAM-treated patients were urinary tract infections (NNH 25) and multiple sclerosis relapse (NNH 100). However, seizure risk has been the focus of concern because of past experience with immediate release fampridine and higher doses of sustained-release FAM. Patients with a history of seizure and evidence of epileptiform activity on EEG were excluded from the trials, so it has been impossible to quantify the actual risk to patients taking FAM 10 mg BID. Accordingly, patients with history of seizure disorder have been contraindicated from taking FAM, and patients should be cautioned to not exceed the maximum recommended semidaily dose. However, prescribing information has not recommended EEG and data are insufficient regarding predictive value of EEG for the occurrence of a first seizure in either a dalfampridine population or a general population.

COMPARATIVE CLINICAL EFFICACY[13, 18, 19]

Relevant Endpoints:

1) Disability

2) Quality of Life

3) Clinical Exacerbation/relapse

4) Withdrawals due to adverse effects

5) Seizure

Study Endpoints:

1) Response to treatment: A timed walk responder is defined as a patient with a faster walking speed, as measured by the T25FW, for at least 3 of 4 visits during the DB treatment period than the maximum speed for any of the first 5 off-drug visits. Clinical significance of the timed-walk response was validated using the MSWS-12
2) Average change from baseline in MSWS-12 score during treatment period.
3) Mean change in walking speed from baseline during the treatment period.

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Evidence Table

Ref./Study Design[1]	Drug Regimens[1]	Patient Population[1,2]	N^	Duration[1]	Efficacy Results[3] (CI, p-values)	ARR/NNT[3, 4]	Safety Results (CI, p-values)	ARR/NNH[3,4]	Quality Rating/Comments[5]
MS-F203 Goodman 33 center Phase III 6/05–6/06 MC, DB, PC, RCT	1. FAM 10 mg BID 2. PLA	Inclusion criteria: • Aged 18–70 • clinically defined multiple sclerosis • able to complete two trials of the T25FW in an average time of 8–45 s at screening Exclusion criteria: • onset of multiple sclerosis exacerbation within 60 days of screening • history of seizures or evidence of epileptiform activity on a screening electroencephalogram • any condition that would interfere with the conduct or interpretation of the study • additional restrictions on changes in concomitant medications to avoid related changes in MS symptoms during the trial Patient characteristics: PLA, FAM total, FAM responders, FAM non-responders Age (mean yrs): 50.9, 51.5, 51.4, 51.6 Female (%): 60, 71, 76, 69 White (%): 93, 93, 91, 93 MS course (%) Relapsing-remitting: 29, 27, 19, 31 Primary progressive: 19, 14, 14, 13 Secondary progressive: 49, 55, 62, 51 Progressive relapsing: 3, 4, 5, 4 Treatment w/ interferon or glatiramer (%): 71, 66, 65, 67 MS duration (mean yrs): 12.7, 13.4, 14.1, 13.1 EDSS score (mean): 5.8, 5.8, 5.8, 5.7	224 72	Treatment period: 14 weeks Phases: 1. Screening 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 3. DB treatment period, beginning 3 weeks after screening: 14 weeks (visits 2 and 3, separated by 2 weeks, and visits 4, 5, and 6, separated by 4 weeks) 4. Non-treatment follow-up, beginning 17 weeks after screening: 4 weeks (visits 7 and 8, separated by 2 weeks)	Timed walk responders (TWR): 1. FAM: 35% [p<0.0001; OR 4.75; CI: 2.08 to 10.86] 2. PLA: 8% Other analyses: Average change from baseline in MSWS-12 score during treatment period, independent of treatment group: Timed walk responders: –6.84 [–9.65 to –4.02, p=0.002] Timed walk non-responders: 0.05 [–1.48 to 1.57] Mean change from baseline in walking speed during treatment period: FAM TWR: 0.51 ft/s [CI: 0.41 to 0.61] FAM TWNR: 0.16 ft/s [CI: 0.11 to 0.21] PLA (TWR + TWNR): 0.1 ft/s [CI: 0.03 to 0.17]	27 / 4	Seizure: 1. FAM: 0.4% (n=1) 2. PLA: 0% Withdrew due to adverse events: 1. FAM: 4.8% 2. PLA: 0%	0.4 / NA 4.8 / 21	**Fair** Internal validity concerns • The definition of a responder seems arbitrary • Appropriateness of questionnaire used to determine clinical significance of findings unclear • Defined ITT population as all randomized patients who had at least one efficacy assessment of T25FW and MSWS-12 during the DB treatment period • Vague exclusion criteria • Did not report how adherence to treatment was ensured, but stated was 97% • Did not state what concomitant medications, other than immunomodulators, or non-pharmacologic therapies patients were using that may have affected mobility • Patients included in the phase II trial, from which the primary endpoint was derived, were required to be able to complete the T25FW in 8–60 s, but in this trial, the requirement was 8–45 s External validity concerns • In speaking of the drug's mechanism of action, the study stated "only some patients would be expected to have axons susceptible to the drug effects at any given time." Therefore, it is unclear which patients at what time would benefit from this medication and at what point patients who had benefited would stop benefiting • Ambulatory deficits in MS caused by multiple factors; unclear which affected by FAM. • Lack of validation of the primary endpoint and unclear clinical significance of the primary endpoint, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Study duration short and lacked follow-up regarding long-term benefit

		T25FW (feet/s): 2.1, 2.1, 2.1, 2.0 LEMMT score: 4, 4.1, 4, 4.1 Ashworth score: 1, 1, 0.9, 0.9 MSWS-12 score: 68.5, 70.7, 70.3, 70.1 SGI score: 4.7, 4.6, 4.6, 4.6							• Patients excluded who have history of seizure and epileptiform activity on EEG • Exclusion criteria so vague that it is unknown whether or not patients who are commonly treated were excluded • Patients predominantly Caucasian • Setting not described
MS-F204									Fair
Goodman 39 center 5/07–2/08 Phase III MC, DB, PC, RCT	1. FAM 10 mg BID 2. PLA	**Inclusion and exclusion criteria similar to MS-F203** **Patient characteristics: PLA, FAM** Age (mean yrs): 51.7, 51.8 Female (%): 62.2, 73.3 White (%): 88.2, 94.2 MS course (%) Relapsing-remitting: 33.6, 35.8 Primary progressive: 17.6, 8.3 Secondary progressive: 47.1, 51.7 Progressive relapsing: 1.7, 4.2 Immunomodulator treatment (%): 83, 83 MS duration (mean yrs): 13.1, 14.43 EDSS score (mean): 5.6, 5.8 T25FW (feet/s): 2.2, 2.1 LEMMT score (mean): 4.0, 3.9 Ashworth score (mean): 0.8, 0.9 MSWS-12 (mean): 67.7, 73.8 SGI score (mean): 4.4, 4.3	119 118	Treatment period: 9 weeks Phases: 1. Pre-screening:1 week 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 3. DB treatment, beginning 3 weeks after screening: 9 weeks (visits 2, 3, 4, 5, and 6 separated by 2 weeks) 4. Follow-up, beginning 12 weeks after screening: 2 weeks (visits 7 & 8, separated by 2 wks)	Timed walk responders: 1. FAM: 42.9% [p<0.0001] 2. PLA: 9.3% Average change from baseline in MSWS-12 during DB treatment period, independent of treatment group: 1. TWR: –6.84 [CI: –9.57 to –2.52, nominal p<0.001] 2. TWNR: 0.85 [CI: –0.72 to 2.43] Average change in walking speed visits 3–6: 1. FAM TWR: 0.51 ft/s (CI: 0.43 to 0.59) 2. FAM TWNR: 0.12 ft/s (CI: 0.05 to 0.19) 3. PLA (TWR + TWNR): 0.17 ft/s [CI: 0.10 to 0.23]	33.6 / 3	Seizure: 1. FAM: 0% 2. PLA: 0.84% (n=1) Withdrawals due to adverse events: 1. FAM: 3.3% 2. PLA: 3.4%	NA NA	• Internal and external validity issues similar to MS-F203, as the two studies principally differed only as follows: shorter duration of DB treatment period (9 weeks v. 14 weeks); 1:1 randomization to active drug and placebo; and an additional visit at the end of the treatment period to obtain data on efficacy and drug plasma concentration near the dosing interval's end. • The FAM group has a higher baseline MSWS-12 score (p=0.006)
MS-F202									Poor
Goodman 24 center Phase II 2/03–12/03 MC, DB, PC, RCT	1. FAM 10 mg BID 2. FAM 15 mg BID 3. FAM 20 mg BID 4. PLA	**Inclusion criteria:** • Aged 18–70 • clinically defined multiple sclerosis • able to complete two trials of the T25FW in an average time of 8–60 s at screening **Exclusion criteria:** • recent MS relapses or changes in medications **Patient characteristics: PLA, FAM 1 mg, FAM 15 mg, FAM 20 mg:** Mean age: 49, 49.8, 47.7, 52.2 % female: 57, 69, 68, 60 % Caucasian: 94, 96, 88, 91 MS course (%) Relapsing-remitting: 28, 19, 30, 16	51 50 57 47	Treatment period: 12 weeks Phases: 1. Screening (visit 0) 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 1 and 2, separated by 1 week) 3. DB dose escalation, beginning 3 weeks after screening: 2 weeks (visits 3 and 4, separated by 1	Mean percent change in walking speed during treatment relative to baseline (placebo run-in) using the T25FW 1. FAM 10 mg: 8% [NS] 2. FAM 15 mg: 11% [NS] 3. FAM 20 mg: 6.5% [NS] 4. PLA: 3% Post-hoc responder analysis (someone whose walking speed for at least three visits during the DB treatment period was faster than the maximum speed measured in the five non-treatment visits):	NA NA NA 27 / 4 28 / 4 30 / 3	Seizure: FAM 10 mg: 0% 2. FAM 15 mg: 0% 3. FAM 20 mg: 0.04% 4. PLA: 0% Withdrawal due to adverse events: 1. FAM 10 mg: 0% 2. FAM 15 mg: 0.02% 3. FAM 20 mg: 0.09% 4. PLA: 0.02%	NA NA 0.04 / NA NA NA 0.07 / NA	Primary endpoint statistical significance not achieved. **Internal validity concerns** • Did not indicate what % of patients were on immunomodulators and what immunomodulators they were on • Did not state what concomitant medications or non-pharmacologic therapies patients were using that may have affected mobility • Allowed changes in dosing of concomitant medications when necessary • Used modified ITT **External validity concerns** • Ambulatory deficits in MS caused by multiple factors; unclear which affected by FAM

		Primary progressive: 26, 23, 24, 26 Secondary progressive: 47, 58, 46, 58 MS duration (mean yrs): 13.9, 10.7, 11.8, 11.8 EDSS score (mean): 5.87, 5.83, 5.64, 5.74 MSFC scores T25FW (feet/s): 1.87, 1.94, 1.99, 2.04 9-HPT (dominant hand, s): 33.9, 35.7, 33.5, 35.3 9-HPT (non-dominant hand, s): 35.7, 30.6, 31.3, 37.2 PASAT-3: 45.7, 49.2, 48.7, 47.5 Composite score: –0.10, 0.04, 0.04, 0.01 LEMMT score: 4.05, 3.98, 4, 3.98 Ashworth score: 1.2, 0.88, 0.89, 0.88 MSWS-12 score: 75.7, 76.3, 74.6, 76.8 CGI score: 3.74, 3.82, 3.8, 3.91 SGI score: 4.38, 4.32, 4.56, 4.25		week) 4. DB stable dose, beginning 5 weeks after screening: 12 weeks (phone visits 5 and 6, separated by 1 week; clinic visits 7, 8, and 9, separated by 4 weeks) 5. Dose reduction, beginning 17 weeks after screening: 1 week (visit 10) 6. Non-treatment washout and follow-up, beginning 18 weeks after screening: 2 weeks (visit 11)	1. FAM 10 mg: 35.3% 2. FAM 15 mg: 36.0% 3. FAM 20 mg: 38.6% 4. PLA: 8.5%				• Clinical significance of the primary endpoint unclear, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Setting from which patients drawn not described • No progressive relapsing patients in the study • Patients predominantly Caucasian • Setting from which patients drawn not described

[1]Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, FAM = fampradine, PLA = placebo
[2]MS disability tests: T25FW: timed 25-foot walk (maximum time allowed to complete is 180 s, or 0.14 ft/s), EDSS: expanded disability status scale, MSFC: MS functional composite, 9-HPT: 9-hole peg test, PASAT: paced auditory serial addition test, LEMMT: lower extremity manual muscle test, MSWS-12: 12-item MS walking scale, SGI: subject global impression (assesses physical wellbeing, 1=terrible to 7=delighted), CGI: clinical global impression (1=not ill to 7=extremely ill)
[3]Results abbreviations: ARR = absolute risk reduction, TWR: timed walk responders, TWNR, timed walk non-responders, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval.
[4]NNT/NNH are reported only for statistically significant results
[5]Quality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
^Modified ITT: all randomized subjects who received at least one efficacy evaluation (T25FW for MS-F202 and 203 and T25FW and MSWS-12 for MS-F204) during the DB period.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):[1]

FAM should not be used in those with a history of seizure or with moderate or severe renal impairment.

Precautions: Those with mild renal impairment may have seizure risk approaching those taking FAM 15 mg bid in clinical trials. FAM should not be taken with any other product containing 4-aminopyridine, such as compounded products. FAM may increase the incidence of urinary tract infections (UTIs).

Tolerability (Drop-out rates, management strategies)

Both the product information sheet and the FDA make it unclear how many MS patients have been exposed to FAM, as the reported figures do not add up. The reported figures are as follows: FAM has been evaluated in 917 MS patients.[1] A total of 601 MS patients have been exposed to FAM for at least 6 months and 405 for at least 1 year, with the majority receiving doses of at least 10 mg bid. A total of 807 MS patients have been exposed to FAM SR (67 in clinical pharmacology trials, 532 in placebo controlled trails, 208 in uncontrolled trials) and 187 patients have been exposed to other forms of FAM, 89 each in clinical pharmacology and in placebo controlled trials.[14]

Despite this lack of clarity, FAM has been used on relatively few patients and that time on the market will tell the prevalence of side effects related to treatment.

In open-label extension studies, a dose-dependent increase in the incidence of seizures was seen in patients with MS at rates of 0.41 per 100 person-years (95% CI 0.13–0.96) for FAM 10 mg twice daily and 1.7 per 100 person-years (95% CI 0.21–6.28) for FAM 15 mg twice daily. Patients with a history of seizures or with evidence of epileptiform activity on EEG were excluded from clinical trials. Therefore, FAM product information states the seizure risk in patients with epileptiform activity is unknown and could be "substantially higher than that observed in FAM clinical studies."[1]

Initially, FAM was studied in MS patients using an immediate release formulation, and seizures occurred in 6/178 patients receiving doses greater than 20 mg/day. This side effect is correlated with plasma concentration. The sustained release formulation was developed as a method to control the fluctuations and high peaks in serum levels seen with the immediate release formulation, and thus serious adverse effects.[14, 20]

Ampyra™ REMS includes a medication guide and annual letters to prescribers and pharmacists describing the proper distribution and safe use of Ampyra™, including warnings about the potential risk of seizure and about the use of compounded formulations.

Adverse events resulted in discontinuation in 4% (15/400) of patients treated with FAM 10 mg twice daily and 2% (5/238) of those treated with placebo.[1]

Pregnancy/Lactation rating:[1] Pregnancy category C. The effects of FAM on labor and delivery are unknown. The safety of FAM in pregnant and nursing women and in patients less than 18 years old has not been tested. FAM should only be used if the benefit justifies the potential risk to the fetus. In animals, FAM given during pregnancy and lactation leads to decreased offspring viability and growth at doses similar to the MRHD.

Unanswered safety questions:
The risk of FAM to patients who are at increased risk for seizures from brain damage, alcohol use, or concurrent use of other medications that decrease the seizure threshold is unknown. Long-term studies are needed to better define the risk of seizures in MS patients. FAM has not been tested in geriatric patients in sufficient number to make a determination about its safety.

Dose Index (efficacy/toxic):[1]
Animal studies have shown no evidence of carcinogenicity at plasma exposures corresponding to 18 times the plasma exposure of humans using the maximum recommended human dose (MRHD), 20 mg daily. However, studies in rats have shown a statistically significant increase in uterine polyps at doses 9 times the MRHD. No evidence of

mutagenicity has been demonstrated from *in vivo* and *in vitro* toxicology assays. No adverse effects on fertility have been observed in male and female rats at doses of 1, 3, and 9 mg/kg/day (relationship to the MRHD not given).

Look-alike / Sound-alike (LA/SA) Error Risk Potential

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexicomp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for dalfamprindine	Delavirdine Desipramine	None		None	None
LA/SA for Ampyra	Anakinra	None		None	None

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ADVERSE REACTIONS[1]

In clinical trials, the most commonly observed adverse reactions—incidence ≥2% and at a rate greater than or equal to placebo—reported in the prescribing information for FAM are presented in the following table.

Adverse Reaction	**Placebo (N=238)**	**FAM 10 mg bid (N=400)**	**NNH**
Urinary tract infection	8%	12%	25
Insomnia	4%	9%	20
Dizziness	4%	7%	33
Headache	4%	7%	33
Nausea	3%	7%	25
Asthenia	4%	7%	33
Back pain	2%	5%	33
Balance disorder	1%	5%	25
Multiple sclerosis relapse	3%	4%	100
Paresthesia	3%	4%	200
Nasopharyngitis	2%	4%	50
Constipation	2%	3%	100
Dyspepsia	1%	2%	100
Pharyngolaryngeal pain	1%	2%	100

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DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg	Extended release tablets	Oral	Twice daily (12 hours apart)	Creatinine clearance should be determined before using FAM. FAM should not be used in those with moderate renal or severe renal impairment*				• May be taken with or without food. • The recommended dose is not to be exceeded. • The FDA has required studies to evaluate the efficacy of lower doses.[13]

*Renally impaired patients would need a dose lower than 10 mg twice daily to avoid the risk of adverse effects such as seizure, and a lower dosage form is unavailable. Seizure risk in patients with mild renal impairment is unknown; however, their FAM plasma levels may approach 15 mg twice daily, a dose that might increase seizure risk.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	96%
Cmax	17.3 ng/mL to 21.6 ng/mL
Protein Binding	1–3%
Elimination	Primarily renal
Half-Life	5.2–6.5 hours
Metabolism	Minor CYP3E1

After 24 hours, 95.9% of a FAM dose is eliminated in the urine 90.3% unchanged, while 0.5% is eliminated in the feces. Two inactive, minor metabolites are produced.

ALLERGIES/INTERACTIONS[1]

Drug-Drug: None

Food-Drug: None

Allergy/Cross Reactive Substances: None

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Appendix 1: Prior Authorization Criteria

Dalfampridine (Ampyra)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization: 2 months (initial) to One year.

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the request for continuation of therapy? (Patient has completed two month trial)	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #5
5. Does the patient have a history of seizures (ICD-9 345.00-345.51, 345.80, 345.81, 780.33-780.39)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #6
6. Does the patient have moderate to severe renal impairment (CrCl <50 ml/min)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Is the patient ambulatory with a walking disability requiring use of a walking aid OR with moderate ambulatory dysfunction who do not require a walking aid AND • Is able to complete the baseline timed 25 foot walk between 8 and 45 seconds	**Yes:** Approve initial fill for 2 month trial.	**No:** Pass to RPH; Deny (medical appropriateness)

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Continuation of Therapy		
1. Has the patient been taking dalfampridine for 2 months or longer and has demonstrated that walking speed has improved while on dalfampridine (documentation of ≥20% improvement in timed 25 foot walk from baseline).	**Yes:** Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

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