


Department of Vermont Health Access

***Therapeutic Class Review
Potassium Channel Blockers***

Overview/Summary

Dalfampridine (Ampyra[®]) is a potassium channel blocker that is Food and Drug Administration (FDA) approved to improve walking in patients with multiple sclerosis (MS).¹ Specifically, dalfampridine is the first agent FDA approved for this indication in MS patients.² Dalfampridine has also been used off-label for the treatment of acute spinal cord injury, dementia and disorders of neuromuscular transmission including myasthenia gravis.³ The mechanism of action by which dalfampridine exerts its therapeutic effects is not fully understood; however, dalfampridine is a broad spectrum potassium channel blocker which has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels in animal studies.¹

Dalfampridine is an extended-release formulation of the agent fampridine (4-aminopyridine, or 4-AP) and is available as 10 mg extended release tablets.³⁻⁴ The FDA required a name change from fampridine to dalfampridine to avoid confusion with an existing agent. It is associated with a dose-dependent increase in the risk of seizures, and is therefore contraindicated in patients with a history of seizure, as well as in patients with moderate to severe renal impairment.¹ Dalfampridine is available as a branded product that is distributed only through specialty pharmacies. Dalfampridine gained FDA approval by demonstrating an increase in walking speed in the timed 25-foot walk, a quantitative mobility and leg function performance test.^{1,4} Results from short-term clinical trials showed that taking dalfampridine 10 mg twice-daily increased walking speed by approximately 25% in responders (patients whose timed 25-foot walk speed was faster for ≥ 3 of four treatment visits compared to five “off-drug” visits) compared to non-responders and placebo ($P < 0.05$ for all comparisons).^{5,6} Patients with all clinical MS subtypes were included in both studies. The role of dalfampridine in the management of MS is not addressed in the current clinical guidelines as the agent was not available when the guidelines were published, but various guidelines support active disease management, treatment of specific MS related symptoms and improving quality of life for patients with MS.⁷⁻⁹ The FDA approved dalfampridine with a Risk Evaluation and Mitigation Strategy program consisting of a patient medication guide and a risk communication plan for patients that is to be distributed to patients treated with dalfampridine.¹⁰

MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.^{7,11-12} This potentially results in the loss of movement and sensation. Walking impairment is one of the clinical hallmark symptoms associated with MS, and approximately 50% of MS patients require some form of walking assistance within 15 years of diagnosis.¹³ The course of MS is unpredictable with variations in severity and progression rate among different patients.² There are four clinical subtypes of MS: relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS) and secondary progressive (SPMS).^{7,11-12} The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.^{7,14} Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.⁷ The approach to treating MS includes management of symptoms, treatment of acute relapses and utilization of disease-modifying therapies to reduce the frequency and severity of relapses and delay disease and disability progression.^{7,11-12}

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Dalfampridine (Ampyra [®])	Potassium channel blockers	-

Indications

Table 2. Food and Drug Administration Approved Indications¹

Generic Name	Improve Walking in Patients with Multiple Sclerosis
Dalfampridine	✓

In addition to its Food and Drug Administration approved indication, dalfampridine has also be used off-label in the treatment of acute spinal cord injury, disorders of neuromuscular transmission and in patients with dementia.³

Pharmacokinetics

Table 3. Pharmacokinetics^{1,3}

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dalfampridine	96	100	90	None	5.2 to 6.5

Clinical Trials

Currently there is limited published clinical trial information regarding the safety and efficacy of dalfampridine. Two randomized, double-blind, placebo controlled trials have been conducted evaluating the efficacy of dalfampridine in improving walking in approximately 540 patients with multiple sclerosis (MS) over 21 and 14 weeks each.⁵⁻⁶ Investigators used the same inclusion criteria for both published trials and all clinical subtypes of MS were included. Patients aged 18 to 70 years with clinically defined MS who were able to complete two trials of the time 25-foot walk in eight to 45 seconds were included. Any patient with an MS exacerbation within the previous 60 days, history of seizure or epileptiform activity on electroencephalogram screening was excluded. The primary efficacy endpoint in both trials was the proportion of patients showing consistent improvement in time 25-foot walk (responders), defined as a patient who experienced faster walking speeds for a ≥ 3 visits out of a possible four during the double-blind treatment period compared to the maximum value achieved in the five non-treatment visits.

In the 21-week trial (N=301), a significantly greater proportion of fampridine-treated patients were considered to be treatment responders compared to placebo treated patients (34.8 vs 8.3%; $P < 0.0001$). The average change from baseline in walking speed for the fampridine treatment responders during the treatment period was 25.2% or 0.51 feet/second compared to 4.7% or 0.10 feet/second for placebo treated patients ($P < 0.001$). More patients treated with fampridine had an increase in walking speed of at least 10% compared to patients treated with placebo ($P = 0.001$). In addition, greater improvements in 12-item MS Walking Scale scores, a rating scale capturing patient perspective on their disability, were observed in the dalfampridine responder group compared to the placebo group ($P = 0.0002$). Scores on the lower extremity manual muscle test were significantly higher for patients treated with fampridine compared to patients treated with placebo ($P = 0.0002$), but no differences were observed between treatment groups in regards to Ashworth scores for spasticity (P value not reported).⁵

In the second trial (N=239), a significantly higher responder rate was reported in patients treated with dalfampridine compared to patients treated with placebo (42.9 vs 9.3%; $P < 0.0001$). The average change from baseline in walking speed for the dalfampridine-treated responders during treatment was 24.7% or 0.51 feet/second (95% confidence interval [CI], 0.43 to 0.59) compared to 7.7% or 0.17 feet/second (95% CI, 0.10 to 0.23) in the placebo group. Patients considered to be non-responders with dalfampridine treatment showed no changes from baseline walking speed compared to placebo (6.0% or 0.12

feet/second; 95% CI, 0.05 to 0.19). Patients randomized to dalfampridine were more likely to achieve a 10% or greater increase in walking speed from baseline compared to placebo ($P=0.002$) and experience greater improvements in lower extremity manual muscle test scores compared to patients treated with placebo ($P=0.028$).⁶

It is important to note that the majority (63%) of patients in both trials were using immunomodulatory drugs, but it is stated that the magnitude of improvement in walking ability was independent of concomitant treatment with these agents.^{1,5-6}

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Goodman et al ⁵ Fampridine SR 10 mg BID vs placebo	DB, MC, PC, PG, RCT Patients 18 to 70 years of age with clinically defined MS who were able to complete two trials of the T25FW in an average time of 8 to 45 seconds at screening	N=301 21 weeks (1 week screening, 2 weeks placebo run-in, 14 weeks DB treatment and 4 weeks no treatment follow-up)	Primary: Response to treatment based on consistent improvement in walking speed (T25FW) defined by a faster walking speed for ≥ 3 of four visits during the treatment period compared to the maximum speed for any of the first five off-drug visits Secondary: Ashworth score for spasticity and LEMMT score	Primary: The proportion of responders was significantly higher in the fampridine group compared to the placebo group (35 vs 8%; $P < 0.0001$) Patients treated with fampridine were more likely to meet the responder criteria compared to patients treated with placebo (OR, 4.75; 95% CI, 2.08 to 10.86). The average change from baseline in walking speed for the fampridine treatment responders during the 14 week treatment period was 25.2% (95% CI, 21.5 to 28.8) or 0.51 feet/second (95% CI, 0.41 to 0.61), compared to 7.5% (95% CI, 5.0 to 10.0) or 0.16 feet/second (95% CI, 0.11 to 0.21) for fampridine non-responders and 4.7% (95% CI, 1.0 to 8.4) or 0.10 feet/second (95% CI, 0.03 to 0.17) for the placebo group. The MSWS-12 rating scale was used as the primary measure to validate the clinical significance of the T25FW response criterion. Average changes from baseline in MSWS-12 scores during the 14 week treatment period were -6.84 (95% CI, -9.65 to -4.02) for fampridine treatment responders, and 0.05 (95% CI, -1.48 to 1.57) for the fampridine non-responders, independent of treatment assignment ($P = 0.0002$). Results indicate a reduced self-assessed ambulation-related disability in timed walk responders. Secondary: Ashworth scores improved in both the fampridine treatment responders and non-responders more than the placebo group, but the differences were not significant. The average improvement in the LEMMT score for fampridine treatment responders during the 14 week treatment period was 0.18 compared with 0.04 for the placebo group ($P = 0.0002$). Fampridine-treated non-responders also had a greater improvement in LEMMT compared to patients receiving placebo (0.11; $P = 0.046$).
Goodman et al ⁶ Dalfampridine ER 10 mg BID	DB, MC, PC, RCT Patients 18 to 70 years of age with	N=239 14 weeks (1 week	Primary: Response to treatment based on consistent	Primary: The proportion of responders was significantly higher in the dalfampridine group compared to the placebo group (42.9 vs 9.3%; $P < 0.0001$) Patients treated with dalfampridine were more likely to meet the responder criteria compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	clinically defined MS who were able to complete the T25FW in an average time of 8 to 45 seconds at screening	screening, 2 weeks placebo run-in, 9 weeks DB treatment and 2 weeks no treatment follow-up)	<p>improvement in walking speed (T25FW) defined by a faster walking speed for ≥ 3 of four visits during the treatment period compared to the maximum speed for any of the first five off-drug visits</p> <p>Secondary: LEMMT scores</p>	<p>patients treated with placebo (OR, 8.14; 95% CI, 3.73 to 17.74).</p> <p>The average change from baseline in walking speed for the dalfampridine-treated responders was 24.7% (95% CI, 21.0 to 28.4) or 0.51 feet/second (95% CI, 0.43 to 0.59) compared to 7.7% of patients treated with placebo (95% CI, 4.4 to 11.0) or 0.17 feet/second (95% CI, 0.10 to 0.23). The dalfampridine-treated non-responders showed no difference in walking speed from baseline compared to the placebo group (6.0%; 95% CI, 2.2 to 9.7 or 0.12 feet/second; 95% CI, 0.05 to 0.19).</p> <p>The average changes from baseline in MSWS-12 scores were -6.04 (95% CI, -9.57 to -2.52) for dalfampridine-treated responders compared to 0.85 (95% CI -0.72 to 2.43) for non-responders to dalfampridine treatment, indicating a reduction in self-assessed ambulatory disability among dalfampridine-treated responders ($P < 0.001$).</p> <p>Secondary: Patients randomized to receive dalfampridine experienced greater improvements in LEMMT scores compared to patients who received placebo (0.145 vs 0.042; $P = 0.028$). Non-responders to dalfampridine treatment did not experience changes in LEMMT that were significantly different from the placebo group (0.048; P value not reported).</p>

Drug regimen abbreviations: BID=twice daily, ER=extended release, SR=sustained release

Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial

Miscellaneous abbreviations: LEMMT=lower extremity manual muscle test, MS=Multiple Sclerosis, MSWS-12=12-item Multiple Sclerosis walking scale, T25FW=Timed 25-foot Walk

Special Populations**Table 5. Special Populations^{1,3}**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dalfampridine	No dosage adjustment required in the elderly. Safety and effectiveness in patients <18 years of age have not been established.	Use is contraindicated in patients with moderate or severe impairment.*	Use has not been evaluated in hepatic impairment. Based on the renal elimination of the agent, a dosage adjustment is not expected.	C	Unknown

* The risk of seizures in patients with mild renal impairment is unknown, but dalfampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures.

Adverse Drug Events

Treatment emergent adverse events that led to discontinuation of therapy in at least two patients treated with dalfampridine include headache, balance disorder, dizziness and confusional state. Commonly reported adverse events occurring in more than 2% of dalfampridine-treated patients and more frequently compared to placebo are provided in Table 6.

Table 6. Adverse Drug Events¹

Adverse Event	Reported Frequency (%)	
	Dalfampridine 10 mg Twice Daily (N=400)	Placebo (N=238)
Asthenia	7	4
Back pain	5	2
Balance disorder	5	1
Constipation	3	2
Dizziness	4	7
Dyspepsia	2	1
Headache	7	4
Insomnia	9	4
Multiple Sclerosis relapse	4	3
Nasopharyngitis	4	2
Nausea	7	3
Paresthesia	4	3
Pharyngolaryngeal pain	1	2
Urinary tract infection	12	8

Contraindications/Precautions

Dalfampridine is contraindicated in patients with a history of seizure and in patients with moderate to severe renal impairment. Additionally, dalfampridine should not be administered with other forms of 4-aminopyridine since the active ingredient is the same.^{1,3}

Urinary tract infections were reported more frequently as adverse reactions in clinical trials in patients treated with dalfampridine 10 mg twice daily compared to patients treated with placebo.^{1,3}

Additionally, this agent is associated with a risk evaluation and mitigation strategy consisting of a patient medication guide and a risk communication plan for patients that is to be distributed to patients treated with dalfampridine.¹⁰

Drug Interactions

No clinically significant drug interactions have been documented with dalfampridine.^{1,3}

Dosage and Administration

Dalfampridine may be administered without regards to meals. Dalfampridine tablets should not be chewed, crushed or otherwise divided due to the extended-release mechanism. Notably, dalfampridine is available through specialty pharmacies, and the Ampyra[®] Patient Support Services will coordinate the distribution of the agent.^{1,13}

Table 7. Dosing and Administration¹

Generic Name	Adult Dose	Pediatric Dose	Availability
Dalfampridine	Improve walking in patients with multiple sclerosis: Extended release tablet: maintenance, 10 mg BID administered 12 hours apart; maximum, 20 mg/day	Safety and effectiveness in patients <18 years of age have not been established.	Extended release tablet: 10 mg

BID=twice daily

Clinical Guidelines

Please note that none of the current clinical guidelines address the role of dalfampridine in the management of multiple sclerosis, as the agent was not available when the guidelines were published.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the Multiple Sclerosis Council for Clinical Practice Guidelines: Disease Modifying Therapies in Multiple Sclerosis (2002) ⁷	<p><u>Interferon β (IFNβ)</u></p> <ul style="list-style-type: none"> It is appropriate to consider IFNβ for treatment in any patient who is at high risk for developing clinically definite multiple sclerosis (MS), or who already has either relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) with relapses. The effectiveness of IFNβ in patients with SPMS but without relapses is uncertain. There is insufficient evidence to determine if certain MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy. It is probable that there is a dose-response curve associated with the use of IFNβ; however, it is possible that a portion of this apparent effect may instead be due to differences in the frequency of IFNβ administration. It is probable that the route of administration of IFNβ is not clinically important; however, the side effect profile does differ between routes of administration. There is no known clinical difference amongst the different types of IFNβ; although, this has not been thoroughly studied. Treatment with IFNβ is associated with the production of neutralizing antibodies (NABs). The rate of NAB production appears to be reduced with IFNβ-1a treatment compared with IFNβ-1b treatment. The biologic effect of NABs is uncertain, but the presence of NABs may be associated with a reduction in clinical effectiveness of IFNβ treatment. <p><u>Glatiramer acetate (GA)</u></p> <ul style="list-style-type: none"> It is appropriate to consider GA for treatment in any patient who has RRMS. GA may also be helpful in patients with progressive disease, but there is no convincing evidence.

Clinical Guideline	Recommendations
<p>Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: Neutralizing Antibody to Interferon β: Assessment of Their Clinical and Radiographic Impact: an Evidence Report (2007)¹⁵</p>	<ul style="list-style-type: none"> • It is probable that the presence of NABs, especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of IFNβ treatment. • It is probable that the rate of NAb production is less with IFNβ-1a treatment compared to IFNβ-1b treatment. However, the magnitude and persistence of any difference in between these forms of IFNβ is difficult to determine. <p>It is probable that the prevalence of NABs to IFNβ is affected by ≥ 1 of the following: formulation, route of administration, dose and/or frequency of administration.</p>
<p>National Clinical Advisory Board of the National Multiple Sclerosis Society: Multiple Sclerosis Disease Management Consensus Statement (2008)⁸</p>	<ul style="list-style-type: none"> • Initiation of treatment with an IFNβ product or GA should be considered as soon as possible following a definite diagnosis of MS with active, relapsing disease. • Initiation of treatment with an IFNβ product or GA may also be considered for select patients with a first attack who are at high risk of MS. • Natalizumab is generally recommended by the Food and Drug Administration (FDA) for patients who have had an inadequate response to, or are unable to tolerate, other MS therapies. • Mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with SPMS who are worsening, whether or not relapses are occurring. • Access to medication should not be limited by the frequency of relapses, age or level of disability. • Treatment should not to be discontinued while insurers evaluate for continuing coverage of treatment. • Therapy should be continued indefinitely, except for the following circumstances: clear lack of benefit, intolerable side effects or availability of better therapy. • The most appropriate agent should be selected on an individual basis. • All FDA-approved agents should be included in formularies and covered so that the most appropriate agent for an individual can be utilized; failure to do so is unethical and discriminatory. • Transition from one disease-modifying agent to another should occur only for medically appropriate reasons. • No therapy has been approved for use by women who are trying to become pregnant, are pregnant or are nursing mothers.
<p>National Institute for Clinical Excellence: Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care (2003)¹⁶</p>	<p><u>Making the diagnosis of MS</u></p> <ul style="list-style-type: none"> • For a patient who presents with a first episode of neurological symptoms, or signs suggestive of demyelination, a diagnosis of MS should be considered. A second episode of neurological symptoms calls for a referral to an appropriate expert for investigation. • A diagnosis of MS is clinical by a doctor with specialist neurological experience, on the basis of evidence of central nervous system lesions scattered in space in time and primarily on the basis of the history and examination. • A patient should be informed of the potential diagnosis of MS as soon as the diagnosis is considered reasonably likely. <p><u>Diagnosis of an acute episode</u></p>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • If a person with MS has a relatively sudden increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis. • Assessment should be undertaken within an appropriate time based on clinical presentation, consider the presence of an acute infective cause and should involve a general practitioner or acute medical/neurological services. • The two specific types of acute clinical syndromes that are recognized include optic neuritis and transverse myelitis. <p><u>Treatment of acute episodes</u></p> <ul style="list-style-type: none"> • A patient experiencing an acute episode that causes distressing symptoms or an increased limitation on activities should be offered a course of intravenous (500 to 1,000 mg) or oral (500 to 2,000 mg) methylprednisolone daily for three to five days. • Frequent or prolonged use of corticosteroids should be avoided. • Other medications for the treatment of acute relapse should not be used unless as part of a formal research protocol. <p><u>Interventions affecting disease progression</u></p> <ul style="list-style-type: none"> • Linoleic acid 17 to 23 g/day may reduce progression of disability. • Azathioprine, mitoxantrone, intravenous immunoglobulin, plasma exchange and intermittent short courses of high-dose methylprednisolone should not be used except in these specific circumstances: after full discussion and consideration of all the risks; with formal evaluation, preferably in a randomized or other prospective trial by an expert in the use of these medicines in MS with close monitoring for adverse events. • Cyclophosphamide, antiviral agents, cladribine, long-term treatment with corticosteroids, hyperbaric oxygen, linomide, whole-body irradiation and myelin basic protein should not be used due to the lack of evidence for beneficial effects on the course of the condition. <p><u>Diagnosis and treatment of specific impairments</u></p> <ul style="list-style-type: none"> • If a patient is diagnosed with significant depression it should be treated appropriately. • At present none of the medications targeted at treating fatigue should be used routinely. Patients should be informed that a small clinical benefit may be gained with amantadine 200 mg/day. • Urgency or urge incontinence should be treated by providing advice on changes to clothing and/or toilet arrangements, intermittent self-catheterization if there is high residual volume, an anticholinergic medication (oxybutynin or tolterodine) and checking for an increased post-voiding residual volume if symptoms recur. • Nocturia should be treated with desmopressin (100 to 400 µg orally or 10 to 40 µg intranasally, at night). • Patients who wish to control urinary frequency during the day, and who have failed with other measures, should be offered desmopressin. Patients should be instructed to never use desmopressin more than once in a 24 hour period. • Patients at risk of urinary tract infections should not be recommended prophylactic use of antibiotics or cranberry juice. • Urinary tract infections should be treated with antibiotics appropriately.

Clinical Guideline	Recommendations
	<p>If more than three infections occur in one year, the patient should be referred to a specialist.</p> <ul style="list-style-type: none"> • Patients who are constipated should be advised on fluid intake and dietary changes that may improve their condition, and then be considered for oral laxatives. • If a patient has apparent constipation despite treatment with oral laxatives he or she should be considered for the routine use of suppositories or enemas. • Motor weaknesses should be managed via exercises and techniques that maximize strength and endurance appropriate to their circumstances. In some patients, equipment may be helpful. • If spasticity or spasms are present, simple causative or aggravating factors such as pain and infection should be sought and treated. • Baclofen or gabapentin should be used initially for bothersome regional or global spasticity or spasms. • Clonazepam, dantrolene, diazepam or tizanidine should be used if baclofen and gabapentin provided no benefit or was associated with intolerable side effects. • Combination of medications, and other medications such as anticonvulsants, should only be used after seeking further specialist advice. • Intramuscular botulinum toxin should not be used routinely for the treatment of spasticity or spasm. It can be considered for relatively localized hypertonia or spasticity that is not responding to other treatments. • Patients who are at risk of developing contractures should consider prolonged stretching using serial plaster casts and other similar methods, such as standing in a standing frame and removable splints. In addition these modalities are usually combined with local botulinum toxin injections and surgery, when necessary. • Patients who experience limitations due to tremor should be assessed by a specialist. • Patients who experience a limitation of activities not otherwise explained should be assessed for sensory losses. • Patients who experience reduced visual acuity, despite using suitable glasses, should be assessed by a specialist. • Patients with nystagmus that causes reduced visual acuity or other visual symptoms should be treated with a time-limited trial of gabapentin. This should be initiated and monitored by a specialist. • Musculoskeletal pain should be managed initially with exercise, passive movement, better seating or other procedures. If these modalities do not provide relief, appropriate analgesic medications should be offered to the patient. • Patients with continued, unresolved, secondary musculoskeletal pain should consider transcutaneous nerve stimulation or antidepressant medications. • Ultrasound, low-grade laser treatment, and anticonvulsants should not be routinely used for the treatment of musculoskeletal pain. • Neuropathic pain should be treated using anticonvulsants or antidepressants. If no benefit is achieved, patients should be assessed by a specialist. • If emotionalism is sufficient to cause concern or distress, a tricyclic antidepressant should be offered to the patient. A selective serotonin

Clinical Guideline	Recommendations
	<p>reuptake inhibitor may also be used.</p> <ul style="list-style-type: none"> • Pharmacologic treatment of anxiety should be with antidepressants or benzodiazepines. • Men with persisting erectile dysfunction and who do not have contraindications should be offered sildenafil 25 to 100 mg. Other specific treatments that can be considered include alprostadil or intracavernosal papaverine. • Pressure ulcers should be dressed according to appropriate local guidelines. • There is some evidence to suggest that the following items might be of benefit; however, due to the lack of evidence there are no strong recommendations made regarding their use: reflexology and massage, fish oils, magnetic field therapy, neural therapy, massage plus body work, t'ai chi and multi-modal therapy.
<p>National Institute for Clinical Excellence: β Interferon and Glatiramer Acetate for the Treatment of Multiple Sclerosis (Appraisal) (2002)⁹</p>	<ul style="list-style-type: none"> • Four general approaches to the treatment of MS, which may be undertaken separately or in combination, include management of symptoms and disability with speech, physio- and occupational therapy and pharmacological or other therapeutic agents; management of emotional and social consequences of relapses and disability; treatment of acute relapses with corticosteroids; and disease modifying treatment targeted at reducing the frequency and/or severity of relapses and/or slowing the progression of the disease. • IFNβ and GA are the only disease modifying agents currently available (Note: this statement is no longer true). • Clinical trials have shown that all three IFNβ products reduce relapse frequency and severity in patients with RRMS and may also influence duration of relapse. The reduction is on average 30%, which is equivalent to approximately one relapse avoided every two and a half years, and has been adequately demonstrated for the first two years of therapy. • The IFNβ products also delay disability progression, but the effects of treatment on disability in the long term, following cessation of therapy, cannot be predicted reliably on the basis of the short-term evidence from clinical trials currently available. • The proposition that the IFNβ products have a positive effect beyond two years is supported by open-label trials. • Betaferon has also been shown to reduce relapse frequency and severity in SPMS. • Clinical trials have shown that GA reduced relapse frequency in patients with RRMS. The reduction is on average 30%, which is equivalent to approximately one relapse avoided every two and a half years, and has been adequately demonstrated for the first two years of therapy. • Data from an open-label, follow-up trial (N=73) of RRMS patients showed that 75% of them were unchanged or improved in terms of accumulation of disability after eight years of treatment with GA.
<p>National Institute for Clinical Excellence: Natalizumab for the Treatment of Adults With High Active Relapsing-Remitting Multiple Sclerosis</p>	<ul style="list-style-type: none"> • Natalizumab is recommended as an option for the treatment only of rapidly evolving severe RRMS, defined as two or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. • Patients currently receiving natalizumab, but for whom treatment would not have been recommended based on the above bullet, should

Clinical Guideline	Recommendations
(Appraisal) (2007) ¹⁷	<p>have the option to continue therapy until they and their clinicians consider it appropriate to stop.</p> <ul style="list-style-type: none"> Natalizumab also has marketing authorization as a single disease modifying therapy in highly active RRMS for patients with high disease activity despite treatment with IFNβ. This group of patients is defined as patients who have failed to respond to a full and adequate course of IFNβ. These patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion. This group of patients is referred to as the “suboptimal therapy group.” Natalizumab has been associated with an increased risk of progressive multifocal leukoencephalopathy. Use may also be associated with infections, urticaria, headache, dizziness, vomiting, nausea, arthralgia, infusion reactions and hypersensitivity reactions.
<p>Association of British Neurologists: Guidelines for Prescribing in Multiple Sclerosis (2009)¹⁸</p>	<ul style="list-style-type: none"> In patients with RRMS and SPMS with superimposed relapses, IFNβ has a consistent effect in reducing relapses (by about one third over two years). This may apply to patients with a clinically isolated syndrome in whom an abnormal magnetic resonance imaging (MRI) indicates a high probability of future conversion to clinically definite MS and patients subsequently meeting the revised McDonald criteria for MS. In patients with RRMS, GA reduces relapse rate by about one third over two years. The IFNβ products and GA may reduce the development of disability through prevention of relapses that would otherwise result in residual dysfunction, although the benefit appears modest at best, and some trials have not shown any benefit. IFNβ and GA do not appear to modify disability progression that is unrelated to relapses. When patients with RRMS are treated with IFNβ and GA, it is not known whether the long term course of multiple sclerosis (beyond five years), is altered. Specifically, it is not established reliably that long-term IFN reduces the accumulation of disability by whatever mechanism or prevents or slows entry to the secondary progressive stage of the disease. In clinically isolated syndromes, IFNβ reduces the conversion rate to MS from 45 to 50% in untreated patients to 28 to 35% over two to three years and GA probably has a similar effect. However, at best, only a marginally significant gain in terms of disability with IFNβ treatment has been demonstrated over three to five years. In patients with rapidly evolving aggressive RRMS, consideration should be given to the use of natalizumab in accordance with National Institute for Clinical Excellence guidelines. In expert centers, various other treatments may also be considered, including mitoxantrone. No treatments have been approved that convincingly alter the course of progressive MS in the absence of relapses after reaching this stage of the disease. As newer treatments emerge and clinical equipoise is agreed between the clinician and patient, participation should be encouraged in clinical trials, rather than open label prescribing.

Conclusions

Ampyra[®] (dalfampridine) is a broad spectrum potassium channel blocker that is Food and Drug Administration (FDA) approved to improve walking in patients with multiple sclerosis (MS).¹ Dalfampridine represents the only agent FDA approved for this specific indication. Walking impairment has been reported in up to 90% of patients with MS, and is one of the most common manifestations of the disease.¹³ Unlike the disease modifying agents that are used to decrease the frequency and/or severity of relapses and/or to slow the progression of MS, dalfampridine is used for the management of symptoms related to MS. Dalfampridine is associated with a dose-dependent risk of treatment emergent seizures and is contraindicated in patients with a history of seizure as well as patients with moderate to severe renal impairment. Dalfampridine is available as a branded, 10 mg extended-release tablet and is currently only available through specialty pharmacies.

Dalfampridine gained FDA approval based on patients' ability to achieve an increase in walking speed in two placebo-controlled trials.^{5,6} In both trials, patients treated with dalfampridine were able to complete the timed 25-foot walk 25% faster, on average, compared to patients treated with placebo. In addition, more patients treated with dalfampridine were able to complete the timed 25-foot walk faster overall, compared to baseline when they received no treatment. The use of dalfampridine in combination with disease-modifying therapies has been shown to be safe and effective, as 63% of patients enrolled in clinical trials were receiving these treatments, with no differences in safety or efficacy noted.¹ Currently there is limited long-term clinical trial information available regarding the safety or efficacy of dalfampridine and none of the current guidelines address its role in the treatment of MS, as the agent was not available when the guidelines were published.

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Ampyra [®]	8	29	100%	\$33,621.16	\$1,159.35
Class Total:	8	29	100%	\$33,621.16	\$1,159.35

Recommendations

In recognition of the following factors:

- The established safety and efficacy of dalfampridine (Ampyra[®]).
- The lack of alternative treatment options that improve walking time in multiple sclerosis patients.
- The safety and efficacy of Ampyra[®] in patients <18 years of age have not been established.

No changes to the current Department of Vermont Health Access (DVHA) Ampyra[®] approval criteria (below) are proposed.

Ampyra[®]

- Patient has a diagnosis of multiple sclerosis.
AND
- Patient age ≥ 18 years.
- Quantity Limit of 2 tablets per day, and a maximum supply per fill of 30 days

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