| Subject: Ampyra (dalfampridine) | Original Effective Date: 5/20/10 |
|---|---|
| Policy Number: MCP-082 | Revision Date(s): 11/21/14 |
| Review Dates: 12/16/15; 9/15/2016; 6/22/2017 | |

## DISCLAIMER

*This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.*

## SUMMARY

This policy addresses the coverage of **Ampyra (dalfampridine)** as a treatment to improve walking in patients with multiple sclerosis (MS) when appropriate criteria are met.

The intent of the Ampyra (dalfampridine) medical coverage policy is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling.

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system. The pathology of MS is characterized by periods of demyelination of nerves leading to nerve damage in both the brain and spinal cord. The repeated episodes of inflammation within the nervous tissue of the brain and spinal cord results in injury to the myelin sheaths and subsequently the nerve cell axons.[A] This potentially results in the loss of movement and sensation throughout the body. Walking impairment is one of the clinical hallmark symptoms associated with MS, and approximately 50% of these patients will require some form of walking assistance within 15 years of diagnosis.[B] Walking impairment has been reported in up to 90% of patients with MS and is one of the most common manifestations of the disease.[B] 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.

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.[5,6] 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.[5,6] The course of MS is unpredictable with variations in severity and progression rate among different patients.[A] Walking impairment has been reported in up to 90% of patients with MS and is one of the most common manifestations of the disease.[8] It is estimated that approximately 50 percent of patients with MS will require the use of a walking aid within 15 to 25 years of diagnosis.[7]

There are four clinical subtypes of MS: relapsing-remitting (RRMS), primary progressive (PPMS), progressive relapsing (PRMS) and secondary progressive (SPMS).[A] The most common form is RRMS, characterized by acute relapses

followed by partial or full recovery.[A] 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. 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.[A]

Dalfampridine (Ampyra®) is the first oral agent approved by the FDA for the treatment of multiple sclerosis (MS) symptoms and is not indicated to decrease relapse rate or prevent the accumulation of disability. Dalfampridine is not a disease modifying therapy (DMT) for MS but targets functional motor impairment. It has the potential to improve walking ability and strengthen the lower leg in people with MS. This may provide patients with the ability to stay independent for longer periods of time and improve quality of life. Approved disease-modifying drugs for MS include interferon beta-1 a (Avonex, Rebif [U.S.]), interferon beta-1b (Betaseron, Extavia [U.S.]), glatiramer (Copaxone), mitoxantrone (Novantrone), and natalizumab (Tysabri).

The mechanism by which Ampyra® exerts its therapeutic effect in MS has not been fully explained. Ampyra is a broad spectrum potassium channel blocker that blocks the exposed potassium channels and restores the action potential and improves neuronal conduction. When the myelin sheath is damaged, potassium may become too active, causing a decrease in nerve function. Dalfampridine blocks potassium from entering the channel, thereby decreasing the disruptions in conduction along the nerves that are associated with functional motor impairment. Dalfampridine is associated with serious adverse events and appears to have dose related adverse events, such as an increase in MS relapse and of seizures.

**CLASSIFICATION:** Potassium Channel blocker

## FDA INDICATIONS

Ampyra (dalfampridine) is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This drug is not indicated to decrease relapse rate or prevent the accumulation of disability.

Available as: 10 mg extended-release tab

FDA Approved: January 22, 2010

Black Box Warnings: *None at the time of this writing*

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.[f]

**RECOMMENDATIONS/COVERAGE CRITERIA**

**Ampyra (dalfampridine)** may be authorized for members who meet **ALL** of the following criteria **[ALL]**

**1. Prescriber specialty [ONE]**

- ❒ Prescribed by, or in consultation* with, a neurologist or a MS specialist. Consultation notes required.

**2. Diagnosis/Indication [ALL]**

- ❒ Diagnosis of multiple sclerosis (MS) **AND** does NOT have a diagnosis of spinal cord injury, myasthenia gravis, demyelinating peripheral neuropathies (such as Guillain-Barré syndrome), Alzheimer's disease, and Lambert Eaton myasthenic syndrome.
  **NOTE:** Documented diagnosis must be confirmed by portions of the individual's medical record, which will confirm the presence of disease and may include, but not limited to, test reports, chart notes from provider's office or hospital admission notes

- ❒ Prescribed for improvement of speed of ambulation

- ❒ Member is ambulatory* AND has an Expanded Disability Status Scale (EDSS)** score **between 2.5 and 6.5**
  **Does not require the use of a wheelchair (bilateral assistance is acceptable, such as a brace, cane, or crutch, as long as the patient can walk 20 meters without resting)*
  ***The Expanded Disability Status Score (EDSS) quantifies disability in eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. EDSS scores 1.0 to 4.5 refer to people with multiple sclerosis who are fully ambulatory. EDSS scores 5.0 to 9.5 are defined by increasing impairment to ambulation.*

- ❒ Baseline timed 25-foot walk test (T25FW) establishing a baseline walking speed **between 8 and 45 seconds**
  **NOTE:** Mobility testing is required for continued coverage. The same test should be performed before and after therapy and shows improvement.
  - ➢ *The Timed 25-Foot Walk (T25FW) is a quantitative measure of lower extremity function. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. In clinical trials, it is recommended that the treating neurologist select the appropriate assistive device for each patient.*

**3. Age/Gender/Other restrictions [ALL]**

- ❒ 18 years of age or older
  - ➢ *Safety and effectiveness of dalfampridine in patients younger than 18 years of age have not been established.*

- ❒ Documentation of significant and continuous walking impairment that impairs ability to complete normal activities of daily living (such as meal preparation, household chores, etc.) attributable to ambulation or functional status despite optimal treatment for Multiple Sclerosis
  **NOTE:** Intermittent occupational tasks that are not required as a daily part of job functioning are not considered instrumental activities of daily living

- ❒ Creatinine clearance greater than 50 mL/minute. Documentation required.
  - ➢ *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.*[a-e]
  - ➢ *Dalfampridine is eliminated by the kidneys. It is, therefore, contraindicated in patients with moderate- to severe kidney impairment. Administration in patients with kidney impairment increases exposure to the drug and may result in increased risk of adverse events, including seizures. The use of Ampyra is contraindicated in patients with moderate or severe renal impairment (CrCl </= 50 mL/min).*

- ❒ No history of a seizure disorder
  - ➢ *Dalfampridine is associated with lowering the seizure threshold and is contraindicated in individuals with a history of a seizure disorder.*

**4. Step/Conservative Therapy/Other condition Requirements [ALL: A, B]**

- ❒ Receiving concurrent therapy with a disease modifying agent for MS (e.g. Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Novantrone, Rebif, Tecfidera, or Tysabri) if indicated
  - ➢ *Dalfampridine can be taken concurrently with disease-modifying therapies for MS.*

**5. Contraindications/Exclusions/Discontinuations**

Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to dalfampridine or 4-aminopyridine
- ❒ Previous or current history of a seizure disorder
  - ➢ *Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.*
- ❒ Moderate or severe renal impairment (CrCl 50 mL/min or less)
  - ➢ *The risk of seizures in patients with mild renal impairment ( CrCl 51-80 ml/min) is unknown, but 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.*

Exclusions [ANY]

- ❒ Co-administration with other forms of 4-aminopyridine (4-AP, fampridine)
  - ➢ *To date, no formal drug interaction studies with dalfampridine have been completed. However, patients should discontinue taking any product containing 4-aminopyridine, such as compounded products, prior to starting dalfampridine since the active ingredient in all of these products is the same. There is potential for dose-related adverse reactions, i.e. seizures.*
- ❒ Unstable disease at the time of initiation (i.e. dose change in DMARD therapy within the past month or evidence of relapse in the past month)
  - ➢ *Patients in the registration trials were allowed to remain on concurrent therapy with DMARDs as long as there had been no dose changes in the previous 6 months.*

**6. Labs/Reports/Documentation required [ALL]**

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

## CONTINUATION OF THERAPY

Ampyra (dalfampridine) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

**1. Initial Coverage Criteria**

- ❑ Member currently meets ALL initial coverage criteria confirmed by documentation

**2. Compliance [ALL]**

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including: [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]
  - ❍ Compliance in taking the medication as prescribed
  - ❍ No intolerable adverse effects or drug toxicity

  **NOTE:** Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

**3. Labs/Reports/Documentation required [ALL APPLICABLE]**

Objective sustained clinical improvement in walking speed of walking ability since initiating treatment with Ampyra (dalfampridine) documented by: [ALL]

- ❒ Improvement of at least 20% in timed walking speed as documented by the T25FW (timed 25-foot walk) from pre-treatment baseline: Most recent T25FW results are: ____seconds on _____(date)
  - ➢ *The ability to walk ≥ 20% faster in the Timed 25-foot walk for patients with MS appears to be clinically meaningful.[3] An analysis of the pooled data from the two clinical trials determined that ≥ 20% increase in walking speed on the timed 25-foot walk was clinically meaningful to patients with MS.[9]*

  **OR**

  Improvement in Expanded Disability Status Scale (EDSS). Baseline score must be between 2.5 and 6.5. Prescriber submit EDSS score before Ampyra: _____ Current EDSS score:_____

- ❒ Functional impairment resolved as a result of increased speed of ambulation resulting in the member being able to complete instrumental activities of daily living (such as meal preparation, household chores, etc.)

**4. Discontinuation of Treatment [ANY]**

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to dalfampridine or 4-aminopyridine
  - ❍ History of seizure
  - ❍ Moderate or severe renal impairment (CrCl 50 mL/min or less)

*NOTE: If member meets any of the discontinuation of treatment criteria, dalfampridine may not be authorized and therapy discontinued. Any symptomatic benefits of the medication will abate over the following 24 hours.*

## ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

### 1. Recommended Dosage [ALL]

- ❑ The recommended dose of dalfampridine is 10mg (one tablet) twice daily, taken every 12 hours (maximum daily dose = 20mg). This dose should not be exceeded. Higher doses have not been shown to be safe and effective.
  - ➢ *No additional benefit was demonstrated at dosages higher than 10mg twice daily, and adverse reactions and discontinuations because of adverse reactions were more frequent at higher dosages.*
  - ➢ *Dalfampridine is eliminated through the kidneys primarily as unchanged drug. Because patients with renal impairment would require a dose lower than 10mg twice daily and no strength smaller than 10mg is available, dalfampridine is contraindicated in patients with moderate to severe renal impairment.*

### 2. Authorization Limit [ALL]

- ❒ Quantity limit: 60 tablets per month

- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time

- ❒ Duration of initial authorization: 12 weeks
  **NOTE:** Physician reassessment by 25-foot walk test (T25FW) should be required after a 12-week trial.
  - ➢ *Approval is initially given for 3 months. If a response is obtained during the first 3 months that the patient is on the medication, medical records documenting this response, including the walking time for the 25 foot walking test after taking Ampyra, along with a new prior authorization request should be submitted by the prescribing physician.*

- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on documented positive clinical response.
  - ➢ *There are no recommended limits on duration of treatment with this medication.*

### 3. Route of Administration [ALL]

- ❒ Ampyra (dalfampridine) is considered an **oral self-administered** medication.

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

## COVERAGE EXCLUSIONS

All other uses of Ampyra (dalfampridine) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

## SUMMARY OF EVIDENCE/POSITION STATEMENTS

- Ampyra (dalfampridine) is the first symptomatic therapy approved for MS patients with impaired walking mobility based on increased speed of walking, in some patients with multiple sclerosis. Dalfampridine is not a disease-modifying agent and, therefore, has not been shown to decrease the number of multiple sclerosis attacks, slow progression of the disease, or improve other symptoms related to multiple sclerosis including fatigue or difficulty with balance. No studies have been performed addressing whether the use of dalfampridine decreases hospitalization rates, reduces resources used for home care, or improves the performance of activities of daily living.

- At the time of this writing, 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. No head-to-head comparisons have been performed between dalfampridine 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.[4]

- Currently, there is limited long-term clinical trial information available regarding the safety or efficacy of dalfampridine considering the length of the pivotal trials, 14 and 9 weeks of active treatment, which is short duration for this expected long-term therapy.

- The role of dalfampridine in the management of MS is not defined within the current clinical guidelines, as dalfampridine was not available when the guidelines were published. Various guidelines support active disease management, treatment of specific MS related symptoms and improving quality of life for patients with MS (Goodin et al, 2002; National Clinical Advisory Board, 2008).[A,C]

Pivotal Trials

Dalfampridine gained FDA approval based on patient's ability to achieve an increase in walking speed in two placebo-controlled trials (Goodman et al, 2009; Goodman et al, 2010).[1,2]

Two phase III, randomized, placebo-controlled, double-blind clinical trials involving a combined total of 540 patients demonstrated improvement in walking. Patients with all clinical MS subtypes were included in both studies. An analysis of the pooled data from the two clinical trials determined that ≥ 20% increase in walking speed on the timed 25-foot walk was clinically meaningful to patients with MS.[9]

- 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 measure of efficacy used in the two pivotal 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.[1] Four feet per second is normal walking speed.
- Using "response to treatment" as the primary efficacy endpoint, the two phase 3 studies compared dalfampridine 10mg bid to placebo and used the change in 12-item MS walking scale (MSWS-12) between baseline and treatment's end to address validity and clinical significance. The MSWS-12 assessed MS patients' perspectives on their ambulatory disability.

Trial 1 (MS-F203)[1] (Goodman AD et al., 2009)

MS-F203 was a randomized, multi-center, double-blind, controlled phase III trial in 301 patients with multiple sclerosis of any type.

The proportion of responders, defined as those whose T25FW time was faster in three of four treatment visits than in any off-treatment visit, was 35% in the treatment group compared to 8% in the placebo group ($p<0.0001$). The 12-item multiple sclerosis walking scale (MSWS-12) was used to validate the clinical significance of response, and responders irrespective of treatment group showed significant score improvement (-6.84 in treatment group versus 0.05 in placebo group, $p=0.0002$). However, additional analysis by the FDA comparing the treatment group to the placebo group showed that although the change in walking speed was statistically significantly higher in those receiving dalfampridine, the clinical significance was questionable as it translated to a 0.88 second difference in the T25FW.

- Trial design: 301 patients were randomized to receive dalfampridine 10 mg or placebo twice daily for 14 weeks.
    - Patients were 18-70 years old (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 with MS exacerbations within 60 days, history of seizure, evidence of epileptiform activity on ECG, or restricted changes in concomitant medications were excluded from the study.
    - 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.
- The primary outcome was percent change in walking speed during treatment relative to baseline.
  The Expanded Disability Status Scale (EDSS)5 is commonly used in MS trials to assess outcome. In the clinical trials of dalfampridine, three key measures were used in addition to the EDSS. The Timed 25-Foot Walk test (T25FW), the 9 hole Peg test and the Paced Auditory Serial Addition test 6. These measures evaluated lower extremity, upper extremity and cognitive function, respectfully. Patients were allowed to use an assistive device as long as it was consistently used across visits.
- Secondary outcome measures of efficacy have included the Ashworth score for spasticity and a lower extremity manual muscle test (LEMMT) done at each visit. The LEMMT measured strength in four muscle groups bilaterally (hip flexors, knee flexors and extensors, and ankle dorsi-flexors). The 12-item multiple sclerosis walking scale (MSWS-12), a rating scale that captures patients' perspectives on their ambulatory disability, was employed to validate the clinical significance of the timed walk test.7 Other secondary validation variables include the subject global impression (SGI) using a seven point scale to describe their impression of the study drug effects over the past week (1=terrible and 7=delighted) and a clinician global impression (CGI)using a seven point scale(1=very much improved to 7=very much worse).
- Results: In a 21 week trial (N=301), the proportion of responders was significantly higher in the fampridine group compared to the placebo group (35 vs 8%; $P<0.0001$). In addition, responders to treatment with fampridine reported a 25% (95% confidence interval [CI], 21.5 to 28.8) increase in timed 25-foot walk speed, on average, compared to 4.7% (95% CI, 1.0 to 8.4) with the placebo group.
    - 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 non-responders 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 2 (MS-F204)[2] (Goodman AD, et al. Ann Neurol 2010; 68(4):494–502)

MS-F204 was another phase III, randomized, double-blind, placebo-controlled trial, the results of which have not yet been published. This trial was similar in design to MS-F203 with the same inclusion and exclusion criteria. The primary difference was a shorter nine week treatment period. The proportion of responders using the same definition as MS-F203 was 42.9% in the treatment group and 9.3% in the placebo group ($p<0.0001$). Additional FDA analysis showed that the difference in 25-foot walk time between the treatment group and the placebo group was only 0.5 seconds.

- Trial design: This trial was similar in overall design to Trial 1, with several specific differences.
  - 239 subjects were randomized in a 1:1 ratio (dalfampridine n = 120; placebo n = 119).
  - The primary outcome was the proportion of patients with >20% improvement on the Timed-25 foot Walk (T25FW). Lower extremity manual muscle test (LEMMT) and the Ashworth Score for spasticity were secondary outcomes.
  - 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. In this 14–week trial (N=239), more patients randomized to receive treatment with dalfampridine were considered responders compared with patients randomized to receive placebo (42.9 vs 9.3%; $P<0.0001$). The average change from baseline in walking speed for the dalfampridine-treated responders was 24.7% (95% CI, 21.0 to 28.4) compared to 7.7% (95% CI, 4.4 to 11.0) for the placebo group.
  - 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).

Conclusion:

- Results from both short-term clinical trials showed that dalfampridine 10mg twice daily increased walking speed by approximately 25% in treatment responders (patients whose timed 25-foot walk speed was faster for three or more of four treatment visits compared to five "off-drug" visits) compared to non-responders and placebo ($P<0.05$ for all comparisons).[1,2]
- 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 while receiving no treatment.
- The ability to walk $\geq$ 20% faster in the Timed 25-foot walk for patients with MS appears to be clinically meaningful.[3]
- 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.

## DEFINITIONS

N/A

## APPENDIX

N/A

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

| CPT | Description |
|---|---|
| | NA-oral administration |

| HCPCS | Description |
|---|---|
| J8499 | Prescription drug, oral, nonchemotherapeutic, NOS |

| ICD-9 | Description [For dates of service prior to 10/01/2015] |
|---|---|
| 340 and 719.7 | Multiple Sclerosis and Difficulty in walking |
| 340 and 781.2 | Multiple Sclerosis and Abnormality of gait |

| ICD-10 | Description [For dates of service on or after 10/01/2015] |
|---|---|
| G35 | Multiple Sclerosis and one of the following codes: |
| R26.2 | Difficulty in walking, not elsewhere classified (Use in conjunction with multiple sclerosis) |
| R26.0 | Ataxic Gait (Use in conjunction with multiple sclerosis) |
| R26.1 | Paralytic Gait (Use in conjunction with multiple sclerosis) |
| R26.81 | Unsteadiness on feet (Use in conjunction with multiple sclerosis) |
| R26.89 | Other abnormalities of gait and mobility (Use in conjunction with multiple sclerosis) |
| R26.9 | Unspecified abnormalities of gait and mobility (Use in conjunction with multiple sclerosis) |

## REFERENCES


**Package Insert, FDA, Drug Compendia**

a. Ampyra (dalfampridine) [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc; January 2014.
b. AHFS Drug Information/Lexicomp. Wolters Kluwer Health. Copyright © 2014. American Society Of Health-System Pharmacists®, Bethesda, MD. Updated periodically. Accessed via subscription: www.statref.com
c. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
d. Drug Facts and Comparisons online. (www.drugfacts.com), Wolters Kluwer Health, St. Louis, MO. Updated periodically.
e. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard. Copyright©2014. URL: http://www.clinicalpharmacology.com.
f. AMPYRA REMS program release. Food and Drug Administration. June 18, 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/022250Orig1s008ltr.pdf. Accessed November 2014.

**Clinical Trials, Definitions, Peer-Reviewed Publications**

1. Goodman AD, Brown TR, Krupp LB,et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. Lancet. 2009;373:732-8.
2. Goodman AD, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol. 2010 Oct; 68(4):494-502.
3. Hobart J, Blight AR, Goodman A, et al. Timed 25-Foot Walk: Direct evidence that improving 20% or greater is clinically meaningful in MS. Neurology. 2013;80:1–9.

4. Rietberg MB, Brooks D, Uitdehaag BMJ et al. Exercise therapy for multiple sclerosis. **Cochrane Database Syst Rev.** 2004, Issue 3. Art. No.: CD003980. DOI: 10.1002/14651858.CD003980.pub2.
5. Courtney AM, Treadaway K, Remington G et al. Multiple Sclerosis. *Med Clin North Am*. 2009; 93(2): 451–476.
6. Calabresi PA. Multiple sclerosis and demyelinating conditions of the central nervous system. In: Goldman L, Ausiello D., eds. Cecil Medicine. 23rd ed. Philadelphia: Saunders Elsevier; 2008. (accessed online from www.mdconsult.com).
7. Snook EM, Moyl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. *Neurorehabil neural repair*. 2009; 23: 108–116.
8. Panitch H, Applebee A. Treatment of walking impairment in multiple sclerosis: an unmet need for a disease-specific disability. Expert Opin Pharmacother. 2011 Jul;12(10):1511-21.
9. Hobart J, Blight AR, Goodman A, et al. Timed 25-Foot Walk: Direct evidence that improving 20% or greater is clinically meaningful in MS. Neurology. 2013;80:1–9.

**Government Agencies, Professional Societies, and Other Authoritative Publications**

A. Goodin DS, Frohman EM, Garmany GP. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the **American Academy of Neurology** and the MS Council for Clinical Practice Guidelines. Neurology. 2002;58(2):169-78.
B. Panitch H, Applebee A. Treatment of walking impairment in multiple sclerosis: an unmet need for a disease-specific disability. Expert Opin Pharmacother. 2011 Jul;12(10):1511-21.
C. **National Clinical Advisory Board** of the National Multiple Sclerosis Society. MS Disease Management Consensus Statement. 2008. Available at: http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/ExpOp_Consensus.pdf. Accessed November 13, 2014

## DISCLAIMER

*This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern.*

*In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.*

*The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.*

*For Molina Medicare members, refer to the Preferred Prior Authorization Criteria below and available at: http://www.cms.hhs.gov/center/coverage.asp .*