**Ampyra™ (dalfampridine)
Prior Authorization with Quantity Limit Program Summary**

This program applies to Medicaid.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing</th>
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</thead>
<tbody>
<tr>
<td>Ampyra®</td>
<td>To improve walking in patients with multiple sclerosis (MS). This was</td>
<td>Maximum recommended dosage is 10 mg twice daily (approximately 12 hours</td>
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<tr>
<td>(dalfampridine)</td>
<td>demonstrated by an increase in walking speed</td>
<td>apart). There is no evidence of additional benefit with doses greater</td>
</tr>
<tr>
<td>tablets</td>
<td></td>
<td>than 10 mg twice daily</td>
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### CLINICAL RATIONALE

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). RRMS is characterized by clearly defined relapses with either full recover or with sequelae and residual deficit upon recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Typically, when SSMS stage is reached, the relapse rate is also reduced. SPMS develops in approximately 90% of patients with RRMS after 25 years and causes the greatest amount of neurologic disability. PPMS represents only about 10 percent of MS cases and is characterized by disease progression from onset, although occasional plateaus, temporary minor improvements, and acute relapses may occur. Many patients with MS develop gait impairment, and some eventually require a cane or wheelchair. Gait impairment in MS can result from a multitude of issues such as spasticity, weakness, fatigue, sensory loss, visual loss, and vestibular dysfunction. Leg weakness and spasticity can result from MS lesions in the descending motor tracts of the brain and spinal cord. Ambulatory imbalance can be caused by lesions involving the cerebellar pathways. Management of gait problems in MS consists mainly of physical therapy along with the use of mobility aids when they become necessary. Dalfampridine, a potassium channel blocker, can improve walking in some patients with MS.
There are several effective disease modifying agents (DMAs) available for RRMS and only one DMA for PPMS. Prior to disease modifying treatments, approximately half of patients diagnosed with relapsing MS would progress to secondary progressive MS by 10 years, and 80-90% would do so by 25 years. Approximately half of patients would no longer be able to walk unaided by 15 years. DMAs reduce but do not eliminate MS relapses and MRI activity. Most of the treatment options for progressive types of MS involve various immunosuppressive therapies, such as azathioprine, cladribine, glucocorticosteroids, cyclophosphamide, cyclosporine, immune globulins, methotrexate, and DMAs. However, nonspecific immunosuppressants may temporarily halt a rapidly progressive course but it is difficult to employ them for more than a few months to a year or two.

The effectiveness of dalfampridine was studied in two phase III, double blind trials. Patient inclusion criteria included the ability to walk 25 feet in 8 to 45 seconds at baseline. Both trials used a responder analysis as the primary endpoint. Responders were defined as patients who achieved faster walking speeds (measured by a timed 25-foot walk in seconds) in at least three of four visits during the study period compared to their fastest speed during the off-treatment period. A retrospective analysis of a previous trial indicated that treatment responders experienced a 25% improvement in walking speed compared to baseline. In trial MS-F203, a total of 35% of patients in the dalfampridine group were responders compared to 8% in the placebo group (p<0.001; OR 4.75; 95% CI 2.08-10.86). The average improvement in walking speed for responders was a 25.5% increase from baseline compared to 4.7% for the placebo group. In trial MS-F204, responder rates were significantly higher in the dalfampridine group (43%) compared to the placebo group (9%) (p<0.01). The mean improvement from baseline walking speed in responders was 21.45% to 26.80% compared to 7.07% to 8.78% in the placebo group.

An FDA analysis using the entire study group (not just responders) found that neither trial demonstrated statistically significant differences in change in walking speed at visit 6 compared to baseline or average walking speed during the treatment phase of the trial. The FDA calculated that changes in walking speed would improve the 25 foot walk time for dalfampridine patients compared to placebo by 0.88 seconds and 0.5 seconds in trials MS-F203 and MS-F204, respectively. FDA analyses found that there was no significant difference between groups in either trial for the SGI score. SGI is a measurement of patient perceived improvement of disease. The FDA analysis did not compare differences in walking endpoints or SGI for the responder group compared to placebo.

Evidence is lacking on how to identify patients that are likely to respond to dalfampridine without a trial of the drug. Dalfampridine is approved to improve walking speed in patients with MS and has not been shown to be effective in improving strength in other neurologic conditions (spinal cord injury, etc.). Evidence supports criteria similar to that used in Phase 3 clinical trials which includes patients diagnosed with MS who have difficulty walking as defined by a timed 25 foot walk between 8 and 45 seconds. The Kurtzke Expanded Disability Status Scale (EDSS) quantifies the level of functioning that is used by health care providers diagnosing MS. The EDSS provides a total score on a scale that ranges from 0 to 10. EDSS 1.0 to 4.5 refer to patients with a high degree of ambulatory ability and subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. A EDSS score of 7 indicates the patient is unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair.

REFERENCES


Ampyra (dalfampridine) Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Ampyra (dalfampridine) Prior Authorization (PA) program is to promote appropriate use according to product labeling and/or clinical guidelines and/or clinical studies. Criteria will approve doses that are at or below the maximum FDA labeled dose.

TARGET AGENT
Ampyra® (dalfampridine)\(^a\)
\(^a\) – generic available

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampyra (dalfampridine)(^a)</td>
<td>62406030007420</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>
\(^a\) – generic available

PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL

Initial Evaluation
Target Agent will be approved when ALL of the following are met:
1. ONE of the following:
   A. The patient has a diagnosis of multiple sclerosis (MS) AND ALL of the following:
      i. If the patient has primary progressive MS (PPMS) or a relapsing form of MS (RRMS), ONE of the following:
         a. There is documentation the patient is receiving concurrent therapy with a disease modifying agent that is appropriate for the patient’s form of MS [e.g. RRMS: Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Lemtrada, Novantrone, Ocrevus, Plegridy, Rebif, Tecfidera, or Tysabri. PPMS: Ocrevus]
         OR
         b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL disease modifying agents appropriate for the patient’s form of MS
      AND
      ii. There is documentation of significant limitations attributable to slow ambulation
      AND
      iii. The patient is ambulatory
      AND
      iv. The prescriber has documented the patient’s baseline timed 25 foot walk AND EDSS score
      OR
   B. The patient has another FDA approved indication for the requested agent
      AND
2. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or has consulted with a specialist in the area of the patient’s diagnosis
   AND
3. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
4. ONE of the following:
A. The requested quantity (dose) does not exceed the program quantity limit
   OR
B. ALL of the following
   i. The requested quantity (dose) is greater than the program quantity limit
      AND
   ii. The requested quantity (dose) requested does not exceed the maximum FDA labeled dose
      AND
   iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 6 months for MS and 12 months for another FDA approved diagnosis

Renewal Evaluation
Target Agent will be approved when ALL of the following are met;
1. The patient has been previously approved for the requested agent through Prime Therapeutics Prior Authorization Review process
   AND
2. ONE of the following:
   a. The patient has a diagnosis of multiple sclerosis AND ALL of the following:
      i. The patient has demonstrated stabilization or improvement from baseline in timed walking speed or EDSS score with the requested agent
      AND
      ii. The patient is ambulatory AND
      iii. The patient has a current documented EDSS score of < 7
   OR
   b. The patient has another FDA approved indication AND has shown stabilization or clinical improvement with the requested agent
   AND
   3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g. neurologist) or has consulted with a specialist in the area of the patient’s diagnosis
   AND
   4. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
   5. ONE of the following:
      a. The requested quantity (dose) does not exceed the program quantity limit
      OR
      b. ALL of the following
         i. The requested quantity (dose) is greater than the program quantity limit
         AND
         ii. The requested quantity (dose) requested does not exceed the maximum FDA labeled dose
         AND
         iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

NOTE: If Quantity Limit program ONLY applies, please refer to Quantity Limit documents.