FEMAAPPROVEDINDICATIONSAND DOSAGE

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

CLINICAL RATIONALE

Multiple Sclerosis

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. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.²

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. 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).²

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. The International Symposium on Gait and balance in Multiple Sclerosis states that the causes of gait and balance dysfunction in patients with MS are multifactorial and therefore may benefit from a wide range of interventions. Evidence based recommendations from the 2nd International Symposium included balance rehabilitation, self-management, medications, functional electrical stimulation, robotics, sensory augmentation, gait training with error feedback, and fall prevention.⁷
**Ampyra**

The effectiveness of Ampyra (dalfampridine) was studied in two adequate and well controlled trials involving 540 patients. Patients in these two clinical trials had a mean Kurtzke Expanded Disability Status Scale (EDSS) score of 6. Patient inclusion criteria in both trials 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.

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

TARGET AGENT
Ampyra® (dalfampridine)

<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)</td>
<td>62406030007420</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

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. ONE of the following:
         1. There is information that the patient is receiving concurrent therapy with a disease modifying agent for the treatment of MS (e.g., Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Gilotop, Lemtrada, Mavenclad, Mayzent, Ocrevus, Plegridy, Rebif, Rituxan, Tecfidera, Tysabri)
      OR
         2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL disease modifying agents FDA labeled for the patient’s indication

      AND
      ii. The prescriber has submitted information that the patient has significant limitations attributable to slow ambulation
      AND
      iii. The patient is ambulatory
      AND
      iv. The prescriber has submitted information documenting 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 the prescriber 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 agent is a generic dalfampridine agent
      OR
      B. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a generic dalfampridine agent that is not expected to occur with 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 for the requested indication
      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 plan’s 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 prescriber has submitted information that the patient has had 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 prescriber has submitted information that the patient has a current EDSS score of < 7
         OR
      B. The patient has another FDA approved indication for the requested agent AND has had 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 the prescriber 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 agent is a generic dalfampridine agent
      OR
      B. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to a generic dalfampridine agent that is not expected to occur with the requested agent
      AND
   6. 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 for the requested indication
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
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

**STEP THERAPY SUPPLEMENT**

**OBJECTIVE**
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

**CONDITIONS FOR APPROVAL**
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

**Length of Approval:** As per program specific criteria