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

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

This is a FlexRx standard and GenRx standard prior authorization program.

FDA APPROVED INDICATIONS AND DOSAGE

FDA Indication: To improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.

Dosing: The maximum recommended dose of dalfampridine is one 10 mg tablet twice daily. The maximum dose should not be exceeded. Doses above the maximum were not shown to confer additional benefit in clinical trials but did increase the incidence of adverse events, including seizures. Doses should be separated by 12 hours.

Dalfampridine is eliminated through the kidneys primarily as unchanged drug. Because patients with renal impairment would require a dose lower than 10 mg twice daily and no strength smaller than 10 mg is available, dalfampridine is contraindicated in patients with moderate to severe renal impairment.

Dalfampridine is also contraindicated in patients with a history of seizure, those who have moderate or severe renal impairment (CrCl ≤50 mL/min), and contraindicated in patients with a history of hypersensitivity to dalfampridine or 4-aminopyridine.

CLINICAL RATIONALE

Dalfampridine (Ampyra)

Dalfampridine was studied in two phase III, double blind trials. Both trials used a responder analysis as the primary endpoint. 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.15

A widely used method to measure the disability status for people with multiple sclerosis (MS) is known as the expanded disability status scale (EDSS). The purpose of this scale is to quantify the level of disability that could be used by health care providers diagnosing MS and monitor changes of disability. The EDSS score ranges from 0 to 10. The first level 1.0 to 4.4 refers to people with high degree of ambulation. Second level from 4.5 to 7.5 refers to patients with impairment to walk. Third level ≥ 7.5 refers to patients with low to no ambulation and usually restricted to a bed or chair.16

**Disease-Modifying Agents**

Disease modifying agents (DMAs) for the treatment of multiple sclerosis (MS) reduce the number and severity of relapses, reduce the number of new lesions appearing on magnetic resonance imaging, and probably reduce long-term progression of MS.5-7 Guidelines from the United States and Europe recommend treatment for relapsing-remitting MS be initiated with either glatiramer or interferon beta (INFβ). Although the INFβ agents differ in route of administration (intramuscular or subcutaneous) and in dosing frequency, studies have not shown clinical differences in efficacy between the different types of INFβ. The INFβ agents are considered appropriate for patients at high risk of developing clinically definite MS, or those who already have relapsing remitting MS or secondary progressive MS and are experiencing relapses. There is a probable dose or frequency of dosing response curve associated with use of INFβ agents. Glatiramer is considered an appropriate option for any patients with relapsing remitting MS. Natalizumab is recommended for patients with relapsing forms of MS who have had an inadequate response to, or are unable to tolerate, other MS therapies.5-7 To date no treatment is approved for treatment of primary progressive multiple sclerosis (PPMS).8-14

**REFERENCES**

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OBJECTIVE
The intent of the Ampyra (dalfampridine) Prior Authorization (PA) program 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. The PA program will consider Ampyra appropriate for patients with multiple sclerosis who are treated by or whose prescribers have consulted with a specialist in the area of the patients’ diagnoses, who have documented significant limitations attributable to slow ambulation, who are receiving a disease modifying agent if indicated, who are ambulatory, and who do not have any FDA labeled contraindications to therapy. The criteria will also allow for a patient who has any FDA approved diagnosis that is not already addressed in the criteria set and who has no contraindications to therapy. The dosing requested for initial therapy for all approvable indications must be at or below the program limit unless it is below the FDA labeled limit and cannot be dose optimized. Renewal criteria include documentation of stabilization or improvement of the baseline walking speed or baseline EDSS score. The renewal dose of Ampyra will have the same restrictions as initial criteria.

TARGET DRUGS AND PROGRAM QUANTITY LIMIT

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Per Day Limit</th>
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</thead>
<tbody>
<tr>
<td>Ampyra (dalfampridine)</td>
<td>62406030007420</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
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PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL
Ampyra will be approved when ALL of the following are met:

1. ONE of the following:
   A. ALL of the following:
      i. The patient has a diagnosis of multiple sclerosis (MS)
      AND
      ii. If the patient has relapsing form of MS, ONE of the following:
          a. The patient is receiving concurrent therapy with a disease modifying agent [e.g. Aubagio, Avonex (IM), Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Lemtrada (IV), Novantrone, Plegridy, Rebif, Tecfidera, or Tysabri (IV)]
          OR
          b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a disease modifying agent
      AND
      iii. 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
      iv. There is documentation of significant limitations attributable to slow ambulation
      AND
      v. BOTH of the following:
         a. The patient is ambulatory
         AND
         b. The prescriber has documented the patient’s baseline timed 25 foot walk AND EDSS score
      OR
   B. The patient has another FDA approved diagnosis
2. The patient does not have any FDA labeled contraindications to therapy with the requested agent

3. One of the following:
   A. The requested quantity (dose) is less than or equal to the program quantity limit
   OR
   B. All of the following
      i. The requested quantity (dose) is above the set limit
      AND
      ii. The requested quantity (dose) requested is at or below the 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 limit

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

Renewal Criteria
1. The patient has been previously approved for therapy through Prime Therapeutics Prior Authorization Review process

2. If the patient has the diagnosis of multiple sclerosis, then the patient has demonstrated a stabilization or improvement from baseline in timed walking speed (timed 25 foot walk) or EDSS score

3. The patient does not have any FDA labeled contraindications to therapy with the requested agent

4. ONE of the following:
   A. The requested quantity (dose) is less than or equal to the program quantity limit
   OR
   B. All of the following
      i. The requested quantity (dose) is above the set limit
      AND
      ii. The requested quantity (dose) requested is at or below the 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 limit

Length of Approval: 12 months

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindication(s)</th>
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<tbody>
<tr>
<td>Ampyra (dalfampridine)</td>
<td>- History of seizures</td>
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<tr>
<td></td>
<td>- Moderate to severe renal impairment (CrCl &lt; 50 mL/min [not an eGFR with this value])</td>
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<td>- hypersensitivity to dalfampridine or 4-aminopyridine</td>
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