Medical Policy

BlueCross BlueShield of Kansas
An Independent Licensee of the Blue Cross and Blue Shield Association

Title: Ampyra™ (dalfampridine)

- **Prime Therapeutics will review Prior Authorization requests.**

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6165KS-AMPY.pdf

  Link to Drug List (Formulary):
  http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
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Institutional
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Current Effective Date: January 1, 1017

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The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

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If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

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' diagnosis, 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.

FDA Approved Indications and Dosage

FDA Indication[1]: To improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.

Dosing[1]: 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.[1]

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.`

POLICY

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)]
         (evidence of a paid claim within the past 30 days, or patient is new to the claim system within the past 120 days AND a statement by the physician that patient is currently taking or has taken a disease modifying agent in the past 30 days, or no evidence of disease modifying agent within the past 30 days)
         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

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

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

Agent	Contraindication(s)
Ampyra (dalfampridine)	▪ History of seizures ▪ Moderate to severe renal impairment (CrCl <50 mL/min [not an eGFR with this value]) ▪ Hypersensitivity to dalfampridine or 4-aminopyridine

Renewal Criteria

1. The patient has been previously approved for therapy through Prime Therapeutics Prior Authorization Review process
   AND
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
   AND
3. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
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

Program Quantity Limits	
Brand (generic)	**Quantity Per Day Limit**
Ampyra (dalfampridine)	
10 mg tablet	2 tablets

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.[2] 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).[3] The average improvement in walking speed for responders was a 25.5% increase from baseline compared to 4.7% for the placebo group.[3] In trial MS-F204, responder rates were significantly higher in the dalfampridine group (43%) compared to the placebo group (9%) ($p<0.01$).[4] 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.[4]

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.[4]

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.[4] FDA analyses found that there was no significant difference between groups in either trial for the SGI score.[4] 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 was 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]

REVISIONS

01-01-2011	Policy added to the bcbsks.com web site.
12-01-2011	Revised Title from "Ampyra™ (dalfampridine) Prior Authorization (with Quantity Limit) Criteria" to "Ampyra™ (dalfampridine) Prior Authorization and Quantity Limit Criteria"
	In Policy section: ▪ Added Gilenya to item #2 to read, "2. The patient is receiving concurrent therapy with a disease modifying agent (e.g. Avonex, Betaseron, Copaxone, Extavia, Gilenya, Novantrone, Rebif, or Tysabri) if indicated" ▪ Revised 7. b. from "The patient has been receiving Ampyra therapy and has demonstrated at least a 20% improvement from baseline in timed walking speed (timed 25 foot walk)" to "The patient is currently receiving Ampyra and has been receiving Ampyra therapy for 2 months or longer AND has demonstrated at least a 20% improvement from baseline in timed walking speed (timed 25 foot walk)"
04-10-2012	Revised Title from "Ampyra™ (dalfampridine) Prior Authorization (and Quantity Limit) Criteria" to "Ampyra™ (dalfampridine) Prior Authorization with Quantity Limit Criteria"
	References updated
05-22-2013	Revised Title from "Ampyra™ (dalfampridine) Prior Authorization (with Quantity Limit) Criteria" to "Ampyra™ (dalfampridine)" ▪ Added under Prior Authorization Form link "Prime Therapeutics will review Prior Authorization requests."
	Removed Target Drugs and Program Quantity Limit chart
	Description section updated to include the addition of FDA Approved Indications and Dosage information
	In Policy section: ▪ In Item 2 added Abagio to read, "2. The patient is receiving concurrent therapy with a disease modifying agent (e.g. Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Novantrone, Rebif, or Tysabri) if indicated" ▪ In Item 5 added "...any contraindication to therapy" and removed, "...a history of seizures AND The patient does not have moderate to severe renal impairment (CrCl [creatinine clearance] less than 50 mL/min; not an eGFR with this value)" to read, "5. The patient does

	not have any contraindication to therapy"
	Added Contraindications chart
	Added Coding section to reflect "There is no specific J code for Ampyra™ (dalfampridine)"
	Rationale section added
	References updated
08-28-2014	This policy was posted July 29,
	Description section updated
	In Policy section: ▪ In Item 2 added "Tecfidera" to the examples of disease modifying agents ▪ In Item 2 added Look-back period information ▪ Added Item 4, "There is documentation of significant limitations of instrumental activities of daily living attributable to slow ambulation" ▪ In Item 5 added "One of the following:" and "The patient has an EDSS of ≥4.5" to read, "ONE of the following: a. The patient is ambulatory with a baseline timed 25 foot walk between 8 to 45 seconds OR b. The patient has an EDSS of ≥4.5" ▪ In Item 6 added "FDA labeled" to read, "The patient does not have any FDA labeled contraindications to therapy" ▪ In Item 7 added "c. The patient has a documented EDSS score of <7" ▪ Revised Length of Approval Initial use from "2 months" to "3 months"
	Updated Rationale section
	Updated References
04-17-2015	Published on 03-17-2015.
	Description section updated
	In Policy section: ▪ In Policy Header added "and Quantity Limit" to read "Prior Authorization and Quantity Limit Criteria for Approval" ▪ Revised to current criteria from: "Ampyra will be approved when ALL of the following are met: 1. The patient has a diagnosis of multiple sclerosis AND 2. The patient is receiving concurrent therapy with a disease modifying agent (e.g. Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Novantrone, Rebif, Tecfidera or Tysabri) if indicated (evidence of a paid claim within the past 30 days, or patient is new to the claim system within the past 120 days AND a statement by the physician that patient is currently taking or has taken a disease modifying agent in the past 30 days, or no evidence of disease modifying agent within the past 30 days) AND 3. The prescriber is a neurologist or has consulted a neurologist AND 4. There is documentation of significant limitations of instrumental activities of daily living attributable to slow ambulation AND 5. ONE of the following: a. The patient is ambulatory with a baseline timed 25 foot walk between 8 to 45 seconds OR b. The patient has an EDSS of ≥4.5 AND 6. The patient does not have any FDA labeled contraindications to therapy AND 7. ONE of the following: a. The patient is being started on initial therapy with Ampyra OR b. The patient is currently receiving Ampyra and has been receiving Ampyra therapy for 2 months or longer AND has demonstrated at least a 20% improvement from baseline in timed walking speed (timed 25 foot walk) OR c. The patient has a documented EDSS score of <7 AND 8. The prescribed dosage is 10 mg twice daily" ▪ In Length of Approval added "…for MS and 12 months for other FDA approved diagnosis"

	to read "Initial use: 3 months for MS and 12 months for other FDA approved diagnosis" ▪ Added Program Quantity Limits chart (this is not new information, but was not reflected in a chart format on the prior version) ▪ In Contraindications chart added, "Hypersensitivity to dalfampridine or 4-aminopyridine"
	Rational section reviewed
	Removed Coding section
	References updated
04-15-2016	Description section updated
	In Policy section: ▪ In Item 1 a ii 1) added "Glatopa" to read, "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)]" ▪ In Item 1 b removed "an" and "labeled" and added "another" and "approved" to read "The patient has another FDA approved diagnosis"
	References updated
01-01-2017	Published 12-20-2016. Effective 01-01-2017.
	Description section updated
	In Policy section: ▪ In Item 1 A iv removed "of instrumental activities of daily living" ▪ In Item 1 A v changed "ONE" to "BOTH" ▪ In Item 1 A v b removed "between 8 to 45 seconds" and added "The prescriber has documented that patient's" and "AND EDSS score" to read "The prescriber has documented the patient's baseline timed 25 foot walk AND EDSS score" ▪ Removed "The patient has a baseline EDSS of ≥4.5 but<7" ▪ Removed Item 1 A vi "ONE of the following: 1) The patient is being started on initial therapy with Ampyra OR 2) The patient is currently receiving Ampyra and has been receiving Ampyra therapy for 2 months or longer AND has demonstrated at least a 20% improvement from baseline in timed walking speed (timed 25 foot walk) OR The patient has a documented stabilization or improvement of their baseline EDSS score (must be <7)" ▪ In Item 2 added "therapy with the requested agent" to read "The patient does not have any FDA labeled contraindications to therapy with the requested agent" ▪ In Length of Approval revised "3" to "6" to read "6 months for MS and 12 months for another FDA approved diagnosis" ▪ Added Renewal Criteria of "1. The patient has been previously approved for therapy through Prime Therapeutics Prior Authorization Review process AND 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 AND 3. The patient does not have any FDA labeled contraindications to therapy with the requested agent AND 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"
04-01-2017	Description section updated
	Rationale section updated

REFERENCES

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