Medical Policy

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

Title: Ampyra™ (dalfampridine)

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth_6165KS_Ampyra.pdf
Prime Therapeutics will review Prior Authorization requests.

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

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

Professional
Original Effective Date: January 1, 2011
Revision Date(s): December 1, 2011; April 10, 2012; May 22, 2013; August 28, 2014
Current Effective Date: August 28, 2014

Institutional
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Revision Date(s): December 1, 2011; April 10, 2012; May 22, 2013; August 28, 2014
Current Effective Date: August 28, 2014

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

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.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

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 (two tablets per day). The PA program will consider Ampyra appropriate for patients with multiple sclerosis treated by a neurologist, or another physician in consultation with a neurologist, who have documented ambulation limitations for activities of daily living, who are receiving a disease modifying agent if indicated, who are ambulatory and able to walk 25 feet in 8 to 45 seconds or an Expanded Disability Status Scale of greater than or equal to 4.5 but less than 7, and who do not have any FDA labeled contraindications to therapy. Renewal criteria include documentation of at least a 20% improvement from baseline in timed walking speed or an EDSS score of less than 7. The dose of Ampyra will be limited to the FDA-labeled dosage of 10 mg twice daily.

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]

POLICY

Prior Authorization Criteria for Approval

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

Length of Approval:
- Initial use: 3 months
- Renewal: 12 months

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

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]

Acorda Therapeutics established the Ampyra First Step Program, which allows patients to receive a free trial of Ampyra. The program allows patients to receive a 2 month supply if they meet the following criteria: cannot have filled an Ampyra prescription within the last 12 months, do not have any history of seizures and do not have moderate or severe kidney impairment, are not allergic to dalfampridine (the active ingredient in Ampyra), and are not a Medicare/Medicaid recipient. Patients must consult a physician prior to receiving the free trial.

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]

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

There is no specific J code for Ampyra™ (dalfampridine)

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

REFERENCES

1. Ampyra prescribing information. Acorda. January 2010.
2. Goodman AD, Brown TR, Cohen JA, et al. Dose comparison trial of sustained release fampridine in multiple sclerosis. Neurology 2008;71:1134-1141.
3. Goodman AD, Brown TR, Krupp LB, et al. Sustained release oral fampridine in multiple sclerosis. Lancet 2009;373:732-738.
4. FDA. Medical review of fampridine. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_MedR.pdf
5. National Multiple Sclerosis Society Disease Management Consensus Statement-Recommendations from the MS Information Sourcebook; 2007 Update. National Multiple Sclerosis Society. Available at: http://www.nationalmssociety.org/for-professionals/healthcare-professionals/publications/expert-opinion-papers/download.aspx?id=8. Accessed January 2, 2009.
6. Goodin DS, Frohman EM, Garmany GP, et al. 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.
7. Prime Therapeutics Formulary Chapter 9.6C Miscellaneous CNS agents: Multiple Sclerosis. December 2008.
8. Avonex prescribing information. Biogen Idec, Inc. October 2012.
9. Betaseron prescribing information. Bayer HealthCare Pharmaceuticals Inc. September 2011.
10. Copaxone prescribing information. Teva Neurosciences, Inc. August 2012.
11. Rebif prescribing information. Serono, Inc./Pfizer Inc. September 2011.
12. Extavia prescribing information. Novartis. March 2012.

13. Tysabri prescribing information. Biogen Idec, Inc./Elan Pharmaceuticals, Inc. August 2012.
14. Gilenya prescribing information. Novartis. May 2012.
15. Pikoulas TE and Fuller MA. Dalfampridine: A Medication to Improve Walking in Patients with Multiple Sclerosis. The Annals of Pharmacotherapy 2012;46:1010-15.
16. Tarver M. Kurtzke Expanded Disability Status Scale. Department of Veterans Affairs. 2009.Available at: http://www.va.gov/MS/articles/Kurtzke_Expanded_Disability_Status_Scale.asp . Accessed October 9, 2013.