LifeWise
Health Plan of Washington

PHARMACY POLICY – 5.01.527
Ampyra (Dalfampridine)

Effective Date:	June 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	May 24, 2024	5.01.565 Pharmacotherapy of Multiple Sclerosis
Replaces:	N/A	

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Introduction

Myelin is a fatty substance that covers and protects nerves. It helps send signals between nerves, and it's the nerves that relay movement instructions to the muscles. Multiple sclerosis damages myelin. This damage interferes with the nerve signals to muscles, including the muscles that are used in walking. Dalfampridine is used to improve the walking ability. It's a potassium channel blocker. That is, it obstructs pores on nerve fibers. This blocking action is thought to improve how electrical signals move along nerves where the signal is weakened because of myelin damage. This drug won't stop the symptoms of multiple sclerosis from getting worse; rather, studies have shown that it increases walking speed. However, it won't work the same for everyone. In some people it won't work at all. This policy describes when dalfampridine or Ampyra may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Dalfampridine (generic)	**Dalfampridine may be considered medically necessary for adult individuals when all of the following criteria are met:** • Individual is 18 years of age or older **AND** • Individual has a diagnosis of multiple sclerosis **AND** • Initial prescription is prescribed by a neurologist **AND** • Individual does not have a history of seizures **AND** • Individual has creatinine clearance (CrCl) greater than 50mL/min **AND** • Individual has completed a baseline timed 25-foot walk (T25FW) **AND** • The dose is limited to 20 mg per day (taken as 10 mg twice daily)
Ampyra (dalfampridine)	**Ampyra (dalfampridine) may be considered medically necessary for adult individuals when all of the following criteria are met:** • Individual is 18 years of age or older **AND** • Individual has a diagnosis of Multiple Sclerosis **AND** • Initial prescription is prescribed by a neurologist **AND** • Individual does not have a history of seizures **AND** • Individual has Creatinine Clearance (CrCl) greater than 50mL/min **AND** • Individual has completed a baseline timed 25-foot Walk (T25FW) **AND** • The dose is limited to 20 mg per day (taken as 10 mg twice daily)

Drug	Medical Necessity
	AND • Individual has tried generic dalfampridine first and had an inadequate response or intolerance to generic dalfampridine (documentation required)

Approval	Criteria
Initial authorization	**Dalfampridine and Ampyra (dalfampridine) may be approved up to 6 months.**
Re-authorization criteria	**Future re-authorization of dalfampridine and Ampyra (dalfampridine) may be approved up to 1 year in duration when clinical benefit/response at the time of re-authorization show:** • Chart notes documenting improvement in the timed 25-foot walk (T25FW) from baseline **AND** • Chart notes documenting recent kidney function with creatinine clearance greater than 50 mL/min

Coding

N/A

Related Information

Benefit Application

Dalfampridine and Ampyra (dalfampridine) are specialty pharmacy drugs managed under the pharmacy benefit.

Evidence Review

Description

It is currently thought that multiple sclerosis (MS) is the result of a combination of factors including immune response, genetics, infection, and environmental issues. MS is characterized by the destruction of the myelin sheath that surrounds axons of the central nervous system (CNS) and eventual axonal damage. This is believed to be an autoimmune attack against myelin and the myelin-producing oligodendrocytes. There is an associated inflammatory response involving B-cells, T-cells, macrophages, antibodies, and complement. The myelin sheath is replaced by sclerotic plaques. The damage to the myelin sheath can delay or halt nerve impulses. Axonal damage leads to loss of nerve impulses.

An estimated 250,000 to 400,000 cases exist in the United States. In 2000, the estimated prevalence was 191/100,000 Caucasians in the United States, with an incidence rate of 7.3/100,000 person-years at risk. Diagnosis usually occurs when individuals are between 20 and 50 years of age. The disease is more prevalent: 1) further away from the equator; 2) in Caucasians; and 3) in women. Other risk factors include Epstein-Barr virus exposure, vitamin D deficiency, and smoking.

MS usually follows one of the following four disease courses, but individual presentation can vary quite widely.

1. Relapsing-remitting MS (RRMS): clearly defined acute attacks followed by periods of partial or full recovery. This is the most common course of the disease describing approximately 85% of MS individuals.

2. Primary-progressive MS (PPMS): the disease steadily progresses although there may be occasional plateaus or remissions. The individual does not experience acute attacks. Approximately 10% of MS individuals have PPMS.

3. Secondary-progressive MS (SPMS): often follows RRMS. Individual experiences acute attacks similar to RRMS, but with progressively less recovery after acute attacks and progressively worsening function between attacks. As with PPMS, there may be occasional plateaus or remissions.

4. Progressive-relapsing MS (PRMS): initially presents as PPMS with steady disease progression, but later experiences acute attacks with followed by partial recovery. This is only seen in approximately 5% of MS individuals.

Rationale

Ampyra (dalfampridine) was approved by the U.S. Food and Drug Administration (FDA) in January 2010 for the indication of improvement in walking of individuals with Multiple Sclerosis (MS) as demonstrated by an increase in walking speed. This approval was based on results from two phase III trials, MS-F203 and MS-F204. The primary endpoint in each of these studies was response to treatment defined as a faster walking time in the timed 25-foot walking test (T25FW) in a majority of on-treatment visits. Using this novel endpoint, 35% of the treatment group in MS-F203 and 42.9% of the treatment group in MS-F204 responded compared to only 8% of the placebo group in MS-F203 and 9.3% of the placebo group in MS-F204 ($p<0.0001$ in each study). However, additional analysis by the FDA showed that the difference in the time needed to complete the timed 25-foot walk between the dalfampridine treatment group and the placebo group was less than one second in each trial.

- MS-F203 was a randomized, multi-center, double-blind, controlled phase III trial in 301 individuals with multiple sclerosis of any type. Individuals were 18-70 years old and able to complete the timed 25-foot walking test with an average time over two trials of 8-45 seconds. Individuals with MS exacerbations within 60 days, history of seizure, evidence of epileptiform activity on ECG, or restricted changes in concomitant medications were excluded from the study. 301 individuals were randomized to receive dalfampridine 10 mg or placebo twice daily for 14 weeks. The proportion of responders, defined as those whose T25FW time was faster in three of four treatment visits than in any off-treatment visit, was 35% in the treatment group compared to 8% in the placebo group ($p<0.0001$). The 12-item multiple sclerosis walking scale (MSWS-12) was used to validate the clinical significance of response, and responders irrespective of treatment group showed significant score improvement (-6.84 in treatment group versus 0.05 in placebo group, $p=0.0002$). However, additional analysis by the FDA comparing the treatment group to the placebo group showed that although the change in walking speed was statistically significantly higher in those receiving dalfampridine, the clinical significance was questionable as it translated to a 0.88 second difference in the T25FW.
- MS-F204 was another phase III, randomized, double-blind, placebo-controlled trial, the results of which have not yet been published. This trial was similar in design to MS-F203 with the same inclusion and exclusion criteria. The primary difference was a shorter nine-week

treatment period. The proportion of responders using the same definition as MS-F203 was 42.9% in the treatment group and 9.3% in the placebo group ($p<0.0001$). Additional FDA analysis showed that the difference in 25-foot walk time between the treatment group and the placebo group was only 0.5 seconds.

- Open-label extension studies of both MS-F203 and MS-F204 were completed. There were 269 individuals that entered MS-F203EXT and 154 individuals that completed it for a maximum exposure of 5 years. For MS-F204EXT there were 214 individuals that entered and 146 individuals that complete it for for a maximum exposure of 3.3 years. No new safety signals emerged and dalfampridine-ER tolerability was consistent with the double-blind phase. Baseline walking speeds for the overall study populations were 2.11 ft/sec in MS-F203EXT and 2.33 ft/sec in MS-F204EXT. Although by 8 weeks, walking speed improved by 0.24 ft/sec and 0.27 ft/sec in these two studies, respectively, the gain in speed gradually diminished, so by the end of the studies, the mean walking speed was similar to or slightly below the baseline level; however, in MS-F203EXT, more than 70% of the enrolled individuals reached the 2-year period with a mean walking speed that remained above the baseline mean.

The primary outcome responder definition from MS-F203 and MS-F204 is based on post-hoc analysis from MS-F202. MS-F202 was a multi-center, randomized, double-blind, placebo-controlled, dose-ranging study. Individuals were 18-70 years of age and able to complete the timed 25-foot walking test with an average time over two trials of 8-60 seconds. Individuals with recent MS relapses or recent medication changes were excluded. Individuals were randomized to receive dalfampridine 10 mg, 15 mg, 20 mg, or placebo twice daily. No difference in change in walking speed was demonstrated between any treatment group and placebo. Post-hoc analysis using responder status as defined in MS-F203 showed responder rates of 35.3%-38.6% in the treatment groups compared to 8.5% in the placebo group. The MSWS-12 scores showed greater improvement in responders irrespective of treatment.

The primary safety concern with dalfampridine is increased risk of seizure, especially at higher doses and plasma concentrations. This led to the development of the sustained-release formulation. Evidence from these trials suggests that there is no difference in seizure risk between dalfampridine 10 mg and placebo. One seizure was observed in a individual receiving dalfampridine 10 mg twice daily in the MS-F203 study, and one seizure was observed in a individual receiving placebo in MS-F204. However, seizure was observed in two individuals receiving dalfampridine 20mg twice daily, just twice the approved dose, in MS-F202. For this reason, dalfampridine is contraindicated in individuals with a history of seizures or moderate or severe renal impairment ($CrCl<50mL/min$).

The Ampyra prescribing information reports the most common adverse events (incidence ≥2% and greater than the placebo rate) as urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

In three placebo-controlled trials (MS-F202, MS-F203, MS-F204), treatment emergent adverse events leading to discontinuation in at least two individuals and leading to discontinuation in individuals treated with D-SR more frequently than with placebo were headache (D-SR 0.5%, placebo 0%), balance disorder (D-SR 0.5%, placebo 0%), dizziness (D-SR 0.5%, placebo 0%), and confusional state (D-SR 0.3%, placebo 0%).

Urinary tract infections were reported more frequently in controlled studies in individuals receiving D-SR than in individuals receiving placebo (12% versus 8%).

2011 Update

Policy updated to include prior authorization criteria for fingolimod.

2012 Update

Recent data do not indicate a need for change to the above medical necessity criteria. Detailed review of new agents for the treatment of MS approved in 2012 will be conducted in early 2013. Meanwhile, these new agents will be covered without requirement for medical necessity review.

2013 Update

Policy update included prior authorization criteria for dimethyl fumarate.

2016 Update

Recent data do not indicate a need for change to the above medical necessity criteria.

2017 Update

Recent data do not indicate a need for change to the above medical necessity criteria.

2018 Update

Re-authorization criteria updated to include reassessment of kidney function at time of request.

2019 Update

Reviewed dalfampridine prescribing information and conducted a primary literature search from 1/1/18 to 3/29/19. No references were found that would impact this policy.

2020 Update

Reviewed dalfampridine prescribing information and no additional FDA-approved indications were identified that would impact this policy.

2021 Update

Reviewed dalfampridine prescribing information and no additional information was identified that would impact this policy.

2022 Update

Reviewed dalfampridine prescribing information and management of gait impairment for individuals with multiple sclerosis. No new information was identified that would impact this policy. Updated the outcomes regarding the open-label extension studies of both MS-F203 and MS-F204.

2023 Update

Reviewed dalfampridine prescribing information and no additional information was identified that would impact this policy.

2024 Update

Reviewed dalfampridine prescribing information and no additional information was identified that would impact this policy.

References

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3. AMCP-formatted Managed Care Dossier: Ampyra (dalfampridine) extended release tablets. February 3, 2010.
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5. Goodman AD, Brown TR, Cohen JA, Krupp LB et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. Neurology 2008;71:1134-41.
6. Goodman AD, Cohen JA, Cross A et al. Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. Multiple Sclerosis 2007; 13: 357-368.
7. Thompson AJ, Hobart JC. Multiple sclerosis: assessment of disability and disability scales. J Neurol 1998; 245: 189-96.
8. Goodman AD, Bethoux F, Brown TR, et al. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: Results of open-label extensions of two Phase 3 clinical trials. Mult Scler. 2015 Sep; 21(10): 1322–1331. doi: 10.1177/1352458514563591
9. Hobart JC, Riazi A, Lamping DL et al. Measuring the impact of MS on walking ability: the 12-item MS Walking Scale. Neurology 2003;60: 31-6.

History

Date	Comments
11/09/10	Add to Prescription Drug Section - New Policy. Reviewed and recommended by P&T on September 26, 2010.
11/10/11	Replace Policy – Policy updated with an additional policy statement: fingolimod (Gilenva) considered medically necessary for treatment of relapsing-remitting MS when criteria are met. Rational updated; references 13-17 added. Reviewed by P&T September 2011.
11/13/12	Replace policy. Policy updated with literature review. Detailed review of new agents for the treatment of MS approved in 2012 will be conducted in early 2013; meanwhile they will be covered without review for medical necessity.
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member's pharmacy benefit; this is now listed in the header and within the coding section.
08/12/13	Replace policy. D*imethyl fumarate (Tecfidera™)* added to the medically necessary policy statement in the treatment of relapsing-remitting multiple sclerosis when criteria are met. Rationale updated; references 19-23 added.
03/10/14	Replace policy. Dimethyl fumarate and fingolimod moved to new policy 5.01.550. Policy title changed from "Oral Agents for the Treatment of Multiple Sclerosis" to "Dalfampridine (Ampyra™)".
04/08/14	Update Related Policies. Add new policy 5.01.550.
08/11/15	Annual Review. A literature search was conducted from 3/1/14-6/30/15. No new studies were found that would require changes to this policy.
01/01/17	Annual Review, approved December 13, 2016. A literature search was conducted from 5/1/15 to 12/5/16. No new studies were found that would require changes to this policy.
09/01/17	Annual Review, approved August 22, 2017. A literature search was conducted from 12/6/16 to 8/14/17. No new studies were found that would require changes to this policy. Title changed from Dalfampridine (Ampyra™) to Ampyra™ (Dalfampridine).
04/01/18	Annual Review, approved March 20, 2018. A literature search was conducted from 8/15/17 to 3/5/2018. No new studies were found that would require changes to this policy. Re-authorization criteria updated and removed table outlining Pharmacologic Treatment Strategies for MS as this policy pertains to Ampyra.
02/01/19	Interim Review, approved January 4, 2019. Added generic dalfampridine and the requirement to use generic dalfampridine prior to brand Ampyra™ (dalfampridine).
05/01/19	Annual Review, approved April 18, 2019. No changes to policy statements.
08/01/20	Annual Review, approved July 23, 2020. No changes to policy statements.
09/01/21	Annual Review, approved August 3, 2021. No changes to policy statements.

Date	Comments
11/01/22	Annual Review, approved October 10, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. No changes to the policy statements.
06/01/24	Annual Review, approved May 24, 2024. No changes to the policy statements.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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