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

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/16/19**
SECTION: DRUGS	**LAST REVIEW DATE: 5/16/19**
	LAST CRITERIA REVISION DATE:
	ARCHIVE DATE:

MAYZENT® (siponimod) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Mayzent (siponimod) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in Neurology or is in consultation with a Neurologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
   - Relapsing forms of multiple sclerosis (MS), including relapsing-remitting disease and active secondary progressive disease such as:
     - Relapsing-remitting MS (RRMS)
     - Secondary-progressive MS (SPMS)
     - Progressive-relapsing MS (PRMS)
   - Clinically isolated syndrome (CIS)

4. Individual has failed, or is intolerant to, or has a contraindication such that the individual is unable to use **ALL** the following preferred step therapy agents:
   - Gilenya (fingolimod)
   - Tecfidera (dimethyl fumarte)
   - Aubagio (teriflunomide)

5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Tested for CYP2C9 variants to determine CYP2C9 genotype
   - Complete blood count within the last 6 months
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin within the last 6 months
   - Electrocardiogram (ECG)
   - Ophthalmologic examination
   - Evidence of varicella zoster virus (VZV) immunity by either a healthcare provider-confirmed history of chickenpox, documented full course of VZV vaccination, **OR** testing for positive antibodies to VZV; any needed vaccination for antibody negative patients to be completed 1 month before initiation

6. There are **NO** contraindications
   - Contraindications include:
     - Patients with a CYP2C9*3/*3 genotype
     - In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
     - Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

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7. Will not be used in individual with significant QT prolongation (QTc > 500 msec), individual on Class Ia or Class III anti-arrhythmic drugs, or New York Heart Association Class II heart failure, unless has been cleared by a Cardiologist

8. Will not be used in individual with complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia unless patient has a functioning pacemaker, unless has been cleared by a Cardiologist

9. Will not be used in patients with an active infection

10. Will not be used with live vaccines during therapy

11. Will not be used concurrently with immune modulating or suppressing agents such as anti-neoplastic drugs, other oral multiple sclerosis medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression) or injectable therapies for multiple sclerosis (e.g., interferon beta-1a or 1b, glatiramer, Lemtrada, Ocrevus, Tysabri, or mitoxantrone)

Initial approval duration: 6 months
Mayzent is initiated with a starter pack that takes into account CYP2C9 genotype
Maintenance dose and duration of titration is determined by CYP2C9 genotype
If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated at day-1 with another starter pack

- **Criteria for continuation of coverage (renewal request):** Mayzent (siponimod) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in Neurology or is in consultation with a Neurologist

2. Individual's condition responded while on therapy
   - Response is defined as:
     - **THREE** of the following:
       - Mild/minimal to no functional neurologic (pyramidal, cerebellar, brainstem, sensory) disabilities
       - Ambulatory without need for assistance
       - Reduction in number of exacerbations or relapses of MS
       - Prolonged time to exacerbation or relapses of MS
       - Reduction in hospitalizations for MS

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section
   - Significant adverse effect such as:

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- Severe, uncontrolled infection
- Macular edema or uveitis
- Serious arrhythmia
- Liver toxicity/injury
- Posterior Reversible Encephalopathy Syndrome
- Progressive Multifocal Leukoencephalopathy

5. Will not be used in individual with significant QT prolongation (QTc > 500 msec), individual on Class Ia or Class III anti-arrhythmic drugs, or New York Heart Association Class II heart failure, unless has been cleared by a Cardiologist

6. Will not be used in individual with complete left bundle branch block, sinus arrest or sino-atrial block, symptomatic bradycardia unless patient has a functioning pacemaker, unless has been cleared by a Cardiologist

7. Will not be used in patients with an active infection

8. Will not be used with live vaccines during therapy

9. Will not be used concurrently with immune modulating or suppressing agents such as anti-neoplastic drugs, other oral multiple sclerosis medications (e.g., Tecfidera, Gilenya, etc., except for Ampyra, which is intended to improve walking speed rather than disease progression) or injectable therapies for multiple sclerosis (e.g., interferon beta-1a or 1b, glatiramer, Lemtrada, Ocrevus, Tysabri, or mitoxantrone)

10. There are no significant interacting drugs

Renewal duration: 12 months

- Mayzent (siponimod) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

MAYZENT® (siponimod) oral tablet (cont.)

Description:

Mayzent (siponimod) is a sphingosine 1-phosphate (S1P) receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Siponimod binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system. Gilenya (fingolimod) is another S1P receptor modulator indicated for the treatment of relapsing forms of MS

MS is a chronic autoimmune disorder of the central nervous system (CNS) in which white blood cells (WBCs) attack and damage the myelin sheath of nerve cells in the CNS. This damage disrupts transmission of nerve impulses. Damage occurs in areas of the brain, spinal cord, and optic nerves. Over time, the damage ultimately leads to progressive physical and cognitive disabilities. The clinical course of MS is highly variable. There are four recognized clinical forms: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). RRMS is the most common form of the disease.

Because MS can affect any area of the brain, optic nerve, or spinal cord, MS can cause almost any neurologic symptom. Patients often present as young adults with two or more clinically distinct episodes of CNS dysfunction with at least partial resolution. Episodes involve numbness, weakness, or incoordination affecting an arm, a leg, or both. Additional symptoms include pain, vertigo, cognitive deficits (such as impaired memory, attention, or judgment), fatigue, speech deficits (such as dysarthria or less commonly aphasia), and bowel, bladder, and sexual dysfunction.

The pathological hallmark of MS is the cerebral or spinal plaque seen on magnetic resonance imaging (MRI). Plaques are discrete regions of demyelination with relative preservation of axons. The neurologic history and physical examination help establish the diagnosis of MS. Diagnostic criteria are symptoms and signs disseminated in time and space (i.e., more than one episode involving more than one area of the CNS). These criteria have been largely replaced by the McDonald criteria, developed in 2001 by the International Panel on the Diagnosis of Multiple Sclerosis. The McDonald criteria retain many features of the original criteria and are intended for use in both clinical practice and clinical trial settings. Diagnoses of “definite MS,” “possible MS,” or, if there is a better explanation for the clinical presentation, “not MS” are determined by findings on clinical exam, MRI, cerebrospinal fluid, and visual evoked potentials. The term “clinically isolated syndrome” (CIS) describes patients who have suffered a first clinical attack but do not meet diagnostic criteria for definite MS. The most recent update in 2010 allows the diagnosis of MS in some patients with CIS.

Multiple observational trials confirm that people with a single clinical demyelinating event with two or more brain or spinal cord lesions remain at increased risk of a future MS diagnosis and are at highest risk within 5 years of the initial event. Evidence from multiple trials confirm that treatment is associated with a significant delay in second clinical relapse or new brain MRI-detected lesions in people with a first demyelinating event who are considered to be at high risk for MS on the basis of brain MRI-detected lesions.

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Definitions:

Forms of Multiple Sclerosis (MS):

Relapsing remitting multiple sclerosis (RRMS)

This form of MS is characterized by acute relapses that are followed by some degree of recovery; patients do not develop worsening of disability between relapses.

Secondary progressive multiple sclerosis (SPMS)

This form of MS is defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. There may, or may not be intermittent relapses, remissions, or periods of temporary minor improvements. As long as the person continues to have relapses, the SPMS course is considered to be both progressive and relapsing.

Progressive relapsing multiple sclerosis (PRMS)

This form of MS is characterized by steadily worsening disease from the beginning, but with occasional relapses along the way. PRMS is considered to be both a progressive and a relapsing form of the disease because people experience steady disease progression and relapses.

Primary progressive multiple sclerosis (PPMS)

This form of MS is defined as progression of disability from onset without superimposed relapses. This type of MS is characterized by a steady decline in function from the beginning without acute attacks. There are no distinct relapses or remissions. This is not a relapsing form of MS.

McDonald criteria:

Clinical Presentation	Additional Data Needed
* 2 or more attacks (relapses) * 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
* 2 or more attacks * 1 objective clinical lesion	Dissemination in space, demonstrated by: * MRI * **or** a positive CSF and 2 or more MRI lesions consistent with MS * **or** further clinical attack involving different site
* 1 attack * 2 or more objective clinical lesions	Dissemination in time, demonstrated by: * MRI * **or** second clinical attack
* 1 attack * 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: * MRI * **or** positive CSF and 2 or more MRI lesions consistent with MS **and** Dissemination in time demonstrated by: * MRI * **or** second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) **and** Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF

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Activities of daily living (ADL):

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

Self-care ADL:

Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

Resources:

Mayzent (siponimod) product information accessed 05-13-19 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=44492772-5aed-4627-bd85-e8e89f308bb3

UpToDate: Symptom management of multiple sclerosis in adults. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/symptom-management-of-multiple-sclerosis-in-adults?source=search_result&search=multiple%20sclerosis%20symptoms&selectedTitle=2~150

UpToDate: Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. Current through Nov 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/disease-modifying-treatment-of-relapsing-remitting-multiple-sclerosis-in-adults?search=multiple%20sclerosis%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H35

National Multiple Sclerosis Society: http://www.nationalmssociety.org/about-multiple-sclerosis/relapsing-ms/index.aspx

McDonald WI, Compston A, Edan G, et al.: Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001; 50 (1):121-127

Polman CH, Reingold SC, Edan G, et al.: Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria." Ann Neurol 2005; 58 (6):840-846

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Polman CH, Reingold SC, Banwell B, et al.: Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria. Annals of Neurology 2011;69:292-302

Rio J, Cornabella M, Montalban X: Multiple sclerosis: Current treatment algorithms. Curr Opin Neurol 2011:24:230-237

Rae-Grant A, Day GS, Marrie RA, et al.: Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018; 90:777-788. doi:10.1212/WNL.0000000000005347

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.