BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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MULTIPLE SCLEROSIS ORAL THERAPY:
AMPYRA (dalfampridine ER)
AUBAGIO (teriflunomide)
BAFIERTAM (monomethyl fumarate)
DALFAMPRIDINE ER
GILENYA (fingolimod)
MAVENCLAD (cladrabine)
MAYZENT (siponimod)
PONVORY (ponesimod)
TECFIDERA (dimethyl fumarate)
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)

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.

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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.**

MAVENCLAD (cladribine)

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

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of relapsing forms of multiple sclerosis (MS), including relapsing-remitting disease and active secondary progressive disease, in patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS
4. Individual does not have clinically isolated syndrome (CIS)
5. Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance to at least 2 alternate drugs indicated for the treatment of MS
6. **ALL** of the following tests have been completed before initiation of **EACH** Treatment Course with continued monitoring as clinically appropriate:
    a. Cancer screening that follows standard screening guidelines for breast, cervical, colorectal, endometrial, lung, prostate, or other type
    b. Negative pregnancy test in a woman of child bearing age
    c. Complete blood count with differential
    d. Lymphocytes must be within normal limits before 1st treatment course and must be at least 800 cells per microliter before 2nd treatment course
    e. A baseline (within 3 months) magnetic resonance imaging prior to the first treatment
    f. Serum aminotransferase, alkaline phosphatase, and total bilirubin
    g. Individual does not have HIV infection
    h. TB screening, if positive, delay Mavenclad (cladrabine) until infection has been treated
    i. Hepatitis B & C screening, if positive, delay Mavenclad (cladrabine) until infection has been treated
    j. Evaluate for acute infection, delay treatment until any active infection is fully controlled
    k. Varicella zoster virus antibody negative individuals must be vaccinated

l. Any needed immunizations that are recommended by immunization guidelines must be given prior to starting Mavenclad (cladrabine) with live-attenuated or live vaccines given at least 4-6 weeks prior to starting Mavenclad (cladrabine)

7. Anti-herpes prophylaxis is used in an individual with lymphocyte count < 200 cell per microliter

8. There are **NO** FDA-label contraindications, such as:
   a. Individual with current malignancy
   b. Woman who is pregnant
   c. Woman of reproductive potential who does not plan to use effective contraception'
   d. Man of reproductive potential who does not plan to use effective contraception
   e. Individual with HIV
   f. Use in an individual with chronic active infections (e.g., hepatitis or tuberculosis)
   g. Woman who is breast feeding an infant or child

9. Individual does not have moderate to severe renal impairment (CrCl < 60 mL/min)

10. Individual does not have moderate to severe hepatic impairment (Child-Pugh score > 6)

11. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

12. There are no significant interacting drugs

Initial approval duration:

- One Treatment Course with two treatment cycles
- **First Treatment Course with two treatment cycles** (**approve at 1.75mg/kg to be administered in two cycles)**
  - First cycle dosage is weight based using 1 or 2 tabs once daily over 4 or 5 days, do not use more than 2 tabs daily
  - Second cycle is separated by 23-27 days of the last dose of a first cycle
- **Second Treatment Course** is given at least 43 weeks after the last dose of the First Treatment Course/Second Cycle and **must fulfill criteria as listed below**
- The safety and efficacy of reinitiating Mavenclad (cladrabine) more than 2 years after completing 2 Treatment Courses has not been studied
- More than 2 Treatment Courses per lifetime **will not** be approved

➢ **Criteria for continuation of coverage (renewal request):** Mavenclad (cladrabine) 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 the patient's diagnosis or is in consultation with a Neurologist

2. Individual successfully completed First Treatment Course

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3. Individual has been adherent with the medication

4. Second Treatment Course to begin at least 43 weeks after the last dose of the First Treatment Course/Second Cycle

5. **ALL** of the required tests as listed in the **Criteria for initial therapy** section have been completed before initiation of **EACH** treatment course with continued monitoring as clinically appropriate:

6. Anti-herpes prophylaxis is used in an individual with lymphocyte count < 200 cell per microliter

7. There are **NO** FDA-label contraindications as listed in the **Criteria for initial therapy** section

8. Individual does not have moderate to severe renal impairment (CrCl < 60 mL/min)

9. Individual does not have moderate to severe hepatic impairment (Child-Pugh score > 6)

10. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

11. There are no significant interacting drugs

Renewal duration:

- One Treatment Course with two treatment cycles
- Second cycle is separated by 23-27 days of the last dose of a first cycle
- Cycle dosage is weight based using 1 or 2 tabs once daily over 4 or 5 days, do not use more than 2 tabs daily
- The safety and efficacy of reinitiating Mavenclad (cladrabine) more than 2 years after completing 2 Treatment Courses has not been studied
- More than 2 Treatment Courses per lifetime **will not** be approved

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-Cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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BAFIERTAM (monomethyl fumarate)
TECFIDERA (dimethyl fumarate)
VUMERITY (diroximel fumarate)

- **Criteria for initial therapy:** Bafiertam (monomethyl fumarate) capsules, Tecfidera (dimethyl fumarate) delayed-release capsules or Vumerity (diroximel fumarate) delayed-release capsules is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

4. **Additional for Vumerity (diroximel fumarate) ONLY:** Documented failure, contraindication per FDA label, intolerance to **ALL** the following: [**Note**: each of the following requires precertification]
    a. Bafiertam (monomethyl fumarate)
    b. Tecfidera (dimethyl fumarate)
    c. Gilenya (fingolimod)
    d. Aubagio (teriflunomide)

5. **Additional for Tecfidera (dimethyl fumarate) ONLY:** Documented failure, contraindication per FDA label, intolerance to dimethyl fumarate generic

6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Complete blood count (CBC) including lymphocyte count
    b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin

7. There are **NO** FDA-label contraindications:
    a. Contraindications for **Bafiertam** (monomethyl fumarate) include:
        i. Known hypersensitivity (e.g., anaphylaxis, angioedema) to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or to any component of the formulation
        ii. Concomitant use with dimethyl fumarate or diroximel fumarate

    b. Contraindications for **Tecfidera** (dimethyl fumarate) include:
        i. Known hypersensitivity to dimethyl fumarate or any of the excipients of Tecfidera

    c. Contraindications for **Vumerity** (diroximel fumarate) include:
        i. Hypersensitivity (e.g., anaphylaxis, angioedema) to diroximel fumarate, Tecfidera (dimethyl fumarate), or to any component of the formulation
        ii. Concomitant use of Tecfidera (dimethyl fumarate)

8. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Bafiertam (monomethyl fumarate) capsules, Tecfidera (dimethyl fumarate) delayed-release capsules or Vumerity (diroximel fumarate) delayed-release capsules 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 the patient's diagnosis or is in consultation with a Neurologist

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

3. Individual has been adherent with the medication, tolerating at least the maintenance dose:
    a. For **Bafiertam** (monomethyl fumarate) dose is at least 190 mg twice daily
    b. For **Tecfidera** (dimethyl fumarate) dose is at least 240 mg twice daily
    c. For **Vumerity** (diroximel fumarate) dose is at least 462 mg twice daily

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Liver toxicity
        ii. Progressive Multifocal Leukoencephalopathy

5. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

GILENYA (fingolimod)
ZEPOSIA (ozanimod)
PONVORY (ponesimod)
MAYZENT (siponimod)

- **Criteria for initial therapy:** Gilenya (fingolimod), Zeposia (ozanimod), Ponvory (ponesimod), or 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 the patient's diagnosis or is in consultation with a Neurologist

  2. **ONE** of the following:
     a. For **Gilenya** (fingolimod)**:** individual is 10 years of age or older
     b. For **Zeposia** (ozanimod), **Ponvory** (ponesimod), or **Mayzent** (siponimod)**:** individual is 18 years of age or older

  3. A confirmed diagnosis of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

  4. **Additional for Zeposia (ozanimod), Ponvory (ponesimod), and Mayzent (siponomid) ONLY:**
     Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance to use **at least two (2)** of the following: [**Note**: each of the following requires precertification]
     a. Avonex
     b. Betaseron
     c. Bafiertam
     d. Copaxone
     e. Plegridy
     f. Rebif
     g. Tecfidera (dimethyl fumarate)
     h. Gilenya (fingolimod)
     i. Aubagio (teriflunomide)

  5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Complete blood count (CBC) within the last 6 months
     b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin within the last 6 months

c. Electrocardiogram (ECG)
d. Ophthalmologic examination
e. 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 of antibody negative patients to be completed 1 month before initiation
f. **Additional for Mayzent** (siponimod) **ONLY:** Tested for CYP2C9 variants to determine genotype

6. There are **NO** FDA-label contraindications:
   a. Contraindications for **each agent** include:
      i. Myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure within the last 6 months
      ii. History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome or sino-atrial block, unless individual has a functioning pacemaker

   b. Contraindications specific for **Gilenya** (fingolimod) include:
      i. Baseline QTc interval $\geq$ 500 msec
      ii. Treatment with Class IA or Class III anti-arrhythmic drugs
      iii. History of a hypersensitivity reaction to fingolimod or any of the excipients in Gilenya

   c. Contraindications specific for **Zeposia** (ozanimod) include:
      i. Severe untreated sleep apnea
      ii. Taking a monoamine oxidase inhibitor

   d. Contraindications specific for **Mayzent** (siponimod) include:
      i. Patients with a CYP2C9*3/*3 genotype

7. Will not be used in the following:
   a. Patients with an active infection

   b. **Additional for Zeposia** (ozanimod) **ONLY:**
      i. Cardiac conduction or rhythm disorders, including significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that could jeopardize the patient's health, unless has been cleared by a Cardiologist
      ii. A resting heart rate of less than 55 bpm at baseline
      iii. Hepatic impairment

   c. **Additional for Ponvory** (ponesimod) **ONLY:**
      i. Patients with moderate or severe hepatic impairment (Child-Pugh Class B and C)
      ii. A patient with a resting heart rate of less than 50 bpm at baseline
      iii. Presence of any severe cardiac disease
      iv. Cardiac conduction or rhythm disorders (including symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmia, cardiac arrest) either in history or observed at screening

v. QTcF interval greater than 470 ms (females) and greater than 450 ms (males) observed at screening
vi. History of syncope associated with cardiac disorders
vii. Uncontrolled systemic arterial hypertension

d. **Additional for Mayzent** (siponimod) **ONLY:**
i. 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
ii. Individual with complete left bundle branch block, sinus arrest or symptomatic bradycardia unless patient has a functioning pacemaker, unless has been cleared by a Cardiologist

8. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Gilenya (fingolimod), Zeposia (ozanimod), Ponvory (ponesimod), or 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 the patient's diagnosis or is in consultation with a Neurologist

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

3. Individual has been adherent with the medication

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

   b. Significant adverse effect such as:
      i. Severe, uncontrolled infection
      ii. Macular edema or uveitis

iii. Serious arrhythmia
iv. Liver toxicity/injury
v. Posterior Reversible Encephalopathy Syndrome
vi. Progressive Multifocal Leukoencephalopathy

5. Will not be used in the following:
   a. Patients with an active infection

   b. With live vaccines during therapy

   c. **Additional for Zeposia** (ozanimod) **ONLY:**
      i. Cardiac conduction or rhythm disorders, including significant QT prolongation (QTcF > 450 msec in males, > 470 msec in females), risk factors for QT prolongation, or other conduction abnormalities or cardiac condition that could jeopardize the patient's health, unless has been cleared by a Cardiologist
      ii. A resting heart rate of less than 55 bpm at baseline
      iii. Hepatic impairment

   d. **Additional for Ponvory** (ponesimod) **ONLY:**
      i. Patients with moderate or severe hepatic impairment (Child-Pugh Class B and C)
      ii. A patient with a resting heart rate of less than 50 bpm at baseline
      iii. Presence of any severe cardiac disease
      iv. Cardiac conduction or rhythm disorders (including symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmia, cardiac arrest) either in history or observed at screening
      v. QTcF interval greater than 470 ms (females) and greater than 450 ms (males) observed at screening
      vi. History of syncope associated with cardiac disorders
      vii. Uncontrolled systemic arterial hypertension

   e. **Additional for Mayzent (siponimod) ONLY:**
      i. 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
      ii. Individual with complete left bundle branch block, sinus arrest or symptomatic bradycardia unless patient has a functioning pacemaker, unless has been cleared by a Cardiologist

6. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

7. There are no significant interacting drugs

Renewal duration: 12 month

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

AUBAGIO (teriflunomide)

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

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin within the last 6 months
     b. Complete blood count (CBC) within the last 6 months
     c. Screening for latent tuberculosis infection with a tuberculin skin test or blood test; if positive, treat tuberculosis with standard medical therapy before use of Aubagio (teriflunomide)
     d. Blood pressure measurement; with elevated blood pressure managed during treatment
     e. Negative pregnancy test in a woman of child bearing potential

  5. There are **NO** FDA-label contraindications, such as:
     a. Severe hepatic impairment (Child-Pugh Class C)
     b. Concurrent use with Arava (leflunomide)
     c. History of a hypersensitivity reaction to Aubagio (teriflunomide), Arava (leflunomide), or to any of the inactive ingredients in Aubagio (teriflunomide)
     d. Woman of child bearing potential who is pregnant or not currently using effective contraception

  6. Will not be used in patients with an active acute or chronic infection

  7. Will not be used with live vaccines during therapy

  8. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

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Initial approval duration: 6 months

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

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

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

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Severe liver injury
        ii. Severe immunodeficiency
        iii. Bone marrow depression
        iv. Severe peripheral neuropathy
        v. Interstitial lung disease, including acute interstitial pneumonitis

5. Will not be used in patients with an active acute or chronic infection

6. Will not be used with live vaccines during therapy

7. Will not be used concurrently with other oral multiple sclerosis medications except for dalfampridine (brand Ampyra or generic), 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) or other immunomodulatory, immuosuppressive or myelosuppressive therapy

8. There are no significant interacting drugs

Renewal duration: 12 months

ORAL THERAPY FOR MULTIPLE SCLEROSIS

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

AMPYRA (dalfampridine ER)
Dalfampridine ER

- **Criteria for initial therapy:** Ampyra (dalfampridine ER) or dalfampridine ER is considered ***medically necessary*** and will be approved with medical record documentation of **ALL** of the following:

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

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of Multiple Sclerosis (MS) in a patient who is still ambulatory and has a baseline timed 25-foot walking speed of between 8-45 seconds **or** has significant limitations of instrumental activities of daily living attributable to slow ambulation

  4. Continues concurrent MS therapy
     a. MS agents may include:
        i. Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Lemtrada, Novantrone, Ocrevus, Plegridy, Rebif, Tysabri, or Zinbryta as indicated

  5. Prescribed dosage will not be greater than 10mg twice daily

  6. The baseline Creatinine clearance (CrCl) is greater than 50 mL/min

  7. Will not be used with Firdapse (amifampridine phosphate) or Ruzurgi (amifampridine)

  8. There are **NO** FDA-label contraindications, such as:
     a. History of seizures or is at high risk for seizures
     b. Moderate to severe renal impairment (CrCl ≤ to 50 mL/min)
     c. Hypersensitivity to Ampyra, dalfampridine, or 4-aminopyrdine (4-AP, fampridine)

  Initial approval duration: 6 months

ORAL THERAPY FOR MULTIPLE SCLEROSIS

- **Criteria for continuation of coverage (renewal request):** Ampyra (dalfampridine ER) or dalfampridine ER 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 neurologic disorders or is in consultation with a Neurologist

  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. Improvement in walking speed of at least 20% over baseline
        ii. Remains ambulatory

  3. Individual has been adherent with the medication **and** the dose does not exceed 10 mg every 12 hours

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

  5. Will not be used with Firdapse (amifampridine phosphate) or Ruzurgi (amifampridine)

  6. There are no significant interacting drugs

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

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.

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 2 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 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.

Mavenclad (cladrabine) is indicated for the treatment of relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of Mavenclad (cladrabine) is recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad (cladrabine) is not recommended for use in patients with CIS because of its safety profile.

Mavenclad (cladrabine) is a nucleoside metabolic inhibitor. The mechanism by which cladribine exerts its therapeutic effects in patients with MS has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. Cladribine is a prodrug that becomes active upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate (Cd-ATP) metabolite.

It is given as two treatment courses, with two treatment cycles per course. The second treatment course is given at least 43 weeks after the last dose of the first course/second cycle. Each cycle is separated by 23-27 days after the last dose of a cycle. Following the administration of 2 treatment courses, do not administer additional Mavenclad (cladrabine) treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. The safety and efficacy of reinitiating Mavenclad (cladrabine) more than 2 years after completing 2 treatment courses has not been studied.

Tecfidera (dimethyl fumarate, DMF) is indicated for the treatment of patients with relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease, in adults. The mechanism by which DMF exerts its therapeutic effect in MS is unknown. DMF and its active metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist *in vitro.* DMF and MMF are postulated to decrease oxidative stress and protect axons from inflammatory mediators. Tecfidera (dimethyl fumarate) is available generically.

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Vumerity (diroximel fumarate) is indicated for the treatment of relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease, in adults. The mechanism by which diroximel fumarate exerts its therapeutic effect in MS is unknown. Diroximel fumarate undergoes rapid pre-systemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). MMF has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans.

Bafiertam (monomethyl fumarate) is indicated for the treatment of relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease, in adults. The mechanism by which monomethylfumarate (MMF) fumarate exerts its therapeutic effect in MS is unknown. MMF has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist *in vitro.* DMF and MMF are postulated to decrease oxidative stress and protect axons from inflammatory mediators.

Gilenya (fingolimod) is a sphingosine 1-phosphate (S1P) receptor modulator indicated for the treatment of patients with relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease in patients 10 years of age or older, to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Gilenya (fingolimod) is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to S1P receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which Gilenya (fingolimod) exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Zeposia (ozanimod), Ponvory (ponesimod) and **Mayzent (siponimod)** are a S1P receptor modulator indicated for the treatment of relapsing forms of MS, including CIS, relapsing-remitting disease, and active secondary progressive disease, in adults. Ozanimod and siponimod bind with high affinity to S1P receptors 1 and 5. Ponesimod binds with high affinity to S1P receptor 1. Ozanimod, ponesimod, and siponimod block the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood.

The mechanism by which ozanimod, ponesimod, and siponimod exert therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

Aubagio (teriflunomide) is a pyrimidine synthesis inhibitor indicated for the treatment of individuals with relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It is the principle active metabolite of Arava (leflunomide) which is indicated for the treatment of rheumatoid arthritis. Teriflunomide is an immunomodulatory agent with anti-inflammatory properties. It inhibits the mitochondrial enzyme involved in pyrimidine synthesis, dihydro-orotate dehydrogenase. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is unknown. It is thought that teriflunomide helps reduce the number of active T and B lymphocytes, two types of WBCs, thought to be particularly damaging in MS.

Ampyra (dalfampridine) and generic dalfampridine are indicated as a treatment to improve walking in adult patients with MS. The mechanism by which dalfampridine exerts its therapeutic effect in MS has not been fully elucidated. Dalfampridine is a broad spectrum potassium channel blocker that blocks the exposed potassium

channels and restores the action potential and improves neuronal conduction. It does not alter the disease course of MS relapse has been reported while on dalfampridine.

Definitions:

Oral Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS):

Oral Agents:
Mavenclad (cladribine)
Dimethyl fumarate (brand Tecfidera and generic)
Vumerity (diroximel fumarate)
Bafiertam (monomethyl fumarate)
Gilenya (fingolimod)
Ponvory (ponesimod)
Zeposia (ozanimod)
Mayzent (siponimod)
Aubagio (teriflunomide)
Adjunct to improve walking speed
Dalfampridine (brand Ampyra and generic)

Forms of multiple sclerosis:

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.

Clinically isolated syndrome (CIS):

A clinical syndrome, that describes patients who demonstrate a first clinical attack but do not meet the diagnostic criteria for definite MS. The McDonald criteria, is a set of criteria used in clinical practice and in clinical trials. It has been updated in 2010 such that it allows the diagnosis of MS in some patients with CIS.

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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

The Child-Pugh classification system:

The Child-Pugh classification is a scoring system used to determine the prognosis of individuals with cirrhosis. Scoring is based upon several factors: albumin, ascites, total bilirubin, prothrombin time, and encephalopathy, as follows:

	Score: 1 point	Score: 2 points	Score: 3 points
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

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

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Kurtzke Expanded Disability Status Scale (EDSS):
A method of quantifying disability in MS. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are:

- Pyramidal
- Cerebellar
- Brainstem
- Sensory
- Bowel and bladder
- Visual
- Cerebral
- Other

EDSS steps of 1.0-4.5 refer to people with MS who are fully ambulatory. EDSS steps of 5.0-9.5 are defined by the impairment to ambulation.

Kurtzke Expanded Disability Status Scale	
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self-care functions
9.0	Confined to bed; can still communicate and eat.

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9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Resources:

Ampyra (dalfampridine) product information, revised by manufacturer Acorda Therapeutics , Inc 09-2017, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Aubagio (teriflunomide) product information, revised by manufacturer Genzyme Corporation 10-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Bafiertam (monmethyl fumarate) product information, revised by manufacturer Banner Life Sciences LLC 04-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 08, 2020.

Dalfampridine product information, revised by manufacturer Sun Pharmaceutical Indus tries , Inc 03-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Dimethyl fumarate product information, revised by manufacturer Mylan Pharmaceuticals Inc 05-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Gilenya (fingolimod) product information, revised by manufacturer Novartis Pharmaceuticals Corporation 12-2019, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Mavenclad (cladrabine) product information, revised by manufacturer EMD Serono, Inc 04-2019, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Mayzent (siponimod) product information, revised by manufacturer Novartis Pharmaceuticals Corporation 07-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Ponvory (ponesimod) product information, revised by manufacturer Janssen Pharmaceutical, Inc. 03-2021, at DailyMed http://dailymed.nlm.nih.gov accessed April 26, 2021.

Tecfidera (dimethyl fumarate) product information, revised by manufacturer Biogen Inc 02-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Vumerity (diroximel fumarate) product information, revised by manufacturer Biogen Inc 08-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.

Zeposia (ozanimod) product information, revised by manufacturer Celgene Corporation 09-2020, at DailyMed http://dailymed.nlm.nih.gov accessed October 9, 2020.