

PHARMACY COVERAGE GUIDELINE

AMPYRA (dalfampridine ER)
AUBAGIO (teriflunomide)
BAFIERTAM (monomethyl fumarate)
Cladribine, generic
Dalfampridine ER, generic
Dimethyl fumarate, generic
Fingolimod, generic
GILENYA (fingolimod)
MAVENCLAD (cladribine)
MAYZENT (siponimod)
PONVORY (ponesimod)
TASCENSO ODT (fingolimod lauryl sulfate)
TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):

- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively “Service”) is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider’s judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member’s benefit plan; and
- Is subject to change as new information becomes available.

Scope

- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance

- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The “[Criteria](#)” section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member’s benefit plan.
- The “[Description](#)” section describes the Service.
- The “[Definition](#)” section defines certain words, terms or items within the policy and may include tables and charts.
- The “[Resources](#)” section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the [request form](#) and provide chart notes, lab workup and any other supporting

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documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements **MAVENCLAD** (cladribine) and **Cladribine** generic

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist

Indication

- A relapsing form of multiple sclerosis (MS), including relapsing remitting disease and active secondary progressive disease, in an individual who has had an inadequate response to, or is unable to tolerate, an alternate drug indicated for the treatment of MS

Age Requirement

- 18 years old and weighs at least 40 kg

Baseline Clinical Evaluation

- Clinical symptoms or attack consistent with demyelinating disease
- MRI of the brain and/or spinal cord was performed and with **ONE** of the following:
 - Magnetic resonance imaging [MRI] is consistent with the diagnosis of MS
 - If an MRI is insufficient for the diagnosis of MS, a cerebrospinal fluid (CSF) evaluation was done and demonstrates CSF specific oligoclonal bands consistent with MS

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- Additional criteria for highly active or aggressive relapsing MS:
 - Demonstrated rapidly advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation severe changes in strength or coordination)
 - Disabling acute relapse(s) with suboptimal response to systemic corticosteroids
 - Multiple relapses (two or more) with incomplete recovery in the ongoing year
 - No response to treatment with one or more disease modifying therapies for at least one year
- Does **NOT** have clinically isolated syndrome (CIS)

Alternative Therapies

- Failure (trial for at least 4 weeks duration), contraindication, intolerance to **BOTH** of the following:
 - Kesimpta (ofatumumab)
 - At least **ONE** of the following:
[Note: Criterion waved for highly active or aggressive relapsing MS OR documented failure of Briumvi, Kesimpta, or Ocrevus due to lack of efficacy]
 1. Teriflunomide (Aubagio or generic)
 2. Glatiramer acetate injection (Copaxone, Glatopa)
 3. **ONE** interferon beta a or beta 1b injection (Avonex, Plegridy, Rebif, Betaseron, Extavia)
 4. **ONE** fumarate (Bafiertam, dimethyl fumarate, Tecfidera, Vumerity)
 5. **ONE** sphingosine 1 phosphate receptor modulator (Fingolimod, Gilenya, Mayzent, Ponvory, Tascenso ODT, Zeposia)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **generic cladribine** for at least three months. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA) (see Definitions section)

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Safety

- Cancer screening per age/gender guidelines
- Negative pregnancy test for women of childbearing age before each treatment course
- Complete blood count with differential before first and second treatment courses
- Lymphocytes within normal limits before first treatment course
- HIV negative
- TB and Hepatitis B & C screening (delay treatment if positive until treated)
- Evaluate and treat any active infection before starting, delay Mavenclad treatment until acute infection is fully controlled
- Varicella zoster virus vaccination if not previously vaccinated
- All needed immunizations completed prior to starting (live vaccines at least 4 to 6 weeks before)
- Baseline MRI within 3 months prior to first treatment course
- Liver function tests: serum aminotransferase, alkaline phosphatase, total bilirubin before each treatment cycle and course
- No FDA label contraindications such as:
 - Current malignancy
 - Pregnancy or lack of effective contraception (women and men of reproductive potential)
 - Active chronic infections (Hepatitis, TB, HIV)
 - Breastfeeding
- Moderate to severe renal impairment (CrCl less than 60 mL/min)
- Moderate to severe hepatic impairment (Child Pugh score greater than 6)
- For lymphocyte count less than 200 cells per microliter, anti herpes prophylaxis must be used
- No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy for other conditions

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Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes
 - Lab results (CBC, liver function, pregnancy test, infection screening)
 - Supporting clinical documentation
 - MRI

Initial Therapy Criteria Approval Duration

- Cumulative dose is 3.5 mg/kg divided into 2 yearly treatment courses (1.75 mg/kg per treatment course) with each course divided into 2 treatment cycles
- Initial approval is One Treatment Course with two treatment cycles
- **First Treatment Course with two treatment cycles**
 - First cycle dosage is weight based and is started at anytime
 - Second cycle is administered 23 to 27 days of the last dose of a first cycle
- OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist

Clinical Response

- Successfully completed first treatment course
- Second treatment course begins at least 43 weeks after last dose of first course

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Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **generic cladribine** for at least three months. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the United States Food and Drug Administration (FDA) (see Definitions section)

Safety

- Cancer screening per age/gender guidelines
- Negative pregnancy test for women of childbearing age before each treatment course
- Complete blood count with differential before first and second treatment courses
- Lymphocytes must be at least 800 cells per microliter before 2nd treatment course
- HIV negative
- TB and Hepatitis B & C screening (delay treatment if positive until treated)
- Evaluate and treat any active infection before starting, delay Mavenclad treatment until acute infection is fully controlled
- Varicella zoster virus vaccination if not previously vaccinated
- Baseline MRI within 3 months prior to first treatment course
- Liver function tests: serum aminotransferase, alkaline phosphatase, total bilirubin before each treatment cycle and course
- No FDA label contraindications or significant adverse drug effects such as:
 - Malignancy
 - Infection
 - Lymphopenia, if recovery takes more than 6 months, discontinue use

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- Other hematologic toxicity (serious decreases in neutrophils, hemoglobin, platelets)
 - Graft versus host disease with blood transfusion
 - Serious liver injury
 - Life threatening acute cardiac failure with myocarditis
 - Progressive multifocal leukoencephalopathy
 - Pregnancy or lack of effective contraception (women and men of reproductive potential)
 - Breastfeeding
 - Moderate to severe renal impairment (CrCl less than 60 mL/min)
 - Moderate to severe hepatic impairment (Child Pugh score greater than 6)
 - For lymphocyte count less than 200 cells per microliter, anti herpes prophylaxis must be used
 - No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy for other conditions

Documentation Requirements

- Chart notes
- Lab results
- MRI report
- Evidence of adherence and absence of contraindications

Continuation Therapy Criteria Approval Duration

- One Treatment Course with two treatment cycles
- **Second Treatment Course with two treatment cycles**
 - First cycle is given at least 43 weeks after the last dose of the prior First Treatment Course/Second Cycle
 - Second cycle is administered 23 to 27 days of the last dose of the first cycle

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Generic Equivalent (if available)

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- The safety and efficacy of reinitiating Mavenclad (cladribine) more than 2 years after completing 2 Treatment Courses has not been studied
 - OR end of plan year

Medical Necessity Requirements for **BAFIERTAM (monomethyl fumarate), **Dimethyl Fumarate** generic, **TECFIDERA** (dimethyl fumarate), and **VUMERITY** (diroximel fumarate)**

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist

Indication

- Relapsing forms of multiple sclerosis (MS), including:
 - Relapsing remitting disease
 - Clinically isolated syndrome (CIS)
 - Active secondary progressive disease

Age Requirement

- 18 years old

Baseline Clinical Evaluation

- Clinical symptoms or attack consistent with demyelinating disease
- MRI of the brain and/or spinal cord was performed and with **ONE** of the following:

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Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

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- Magnetic resonance imaging [MRI] is consistent with the diagnosis of MS
 - If an MRI is insufficient for the diagnosis of MS, a cerebrospinal fluid (CSF) evaluation was done and demonstrates CSF specific oligoclonal bands consistent with MS
 - Complete blood count with differential
 - Liver function tests: serum aminotransferase, alkaline phosphatase, total bilirubin

Brand Specific Criteria

- **For Tecfidera (dimethyl fumarate) or other generic dimethyl fumarate:** Documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic dimethyl fumarate by CIVICASRIPT**
- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications:
 - Known hypersensitivity to fumarate products
 - Combination of fumarate products
- No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy for other conditions
- **For Vumerity:** No moderate or severe renal impairment (i.e., creatinine clearance of less than 60 mL/min)

Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes

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- Lab results (CBC, liver function, pregnancy test)
 - Supporting clinical documentation
 - MRI

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist

Clinical Response

- Achieves and maintains **TWO** of the following:
 - Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
 - Clinically stable neurologic exam
 - Reduction in number of exacerbations or relapses of MS
 - Prolonged time to exacerbation or relapses of MS
 - Reduction in use of high dose steroids or hospitalizations for MS

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

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- **For Tecfidera (dimethyl fumarate) or other generic dimethyl fumarate:** Documented failure, contraindication per FDA label, intolerance, or is not a candidate for **generic dimethyl fumarate by CIVICASRIPT**
 - Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications or significant adverse effects such as:
 - Known hypersensitivity to fumarate products (i.e., anaphylaxis, angioedema)
 - Combination of fumarate products
 - Liver toxicity
 - Progressive Multifocal Leukoencephalopathy
 - Serious gastrointestinal reactions, including perforation, ulceration, hemorrhage, and obstruction
- No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy for other conditions
- **For Vumerity:** No moderate or severe renal impairment (i.e., creatinine clearance of less than 60 mL/min)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use (CBC, liver function tests)

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

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- If criteria for response to therapy is not met, consider changing disease modifying therapy

Medical Necessity Requirements for Fingolimod generic, GILENYA (fingolimod), TASCENSO ODT (fingolimod lauryl sulfate), MAYZENT (siponimod), and PONVORY (ponesimod)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist

Indication

- Relapsing forms of multiple sclerosis (MS) including:
 - Relapsing remitting disease
 - Clinically isolated syndrome (CIS)
 - Active secondary progressive disease

Age Requirement

- Consistent with product labeling

Baseline Clinical Evaluation

- Clinical symptoms or attack consistent with demyelinating disease
- MRI of the brain and/or spinal cord was performed and with **ONE** of the following:
 - Magnetic resonance imaging [MRI] is consistent with the diagnosis of MS

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- If an MRI is insufficient for the diagnosis of MS, a cerebrospinal fluid (CSF) evaluation was done and demonstrates CSF specific oligoclonal bands consistent with MS
 - Complete blood count with differential
 - Liver function tests: serum aminotransferase, alkaline phosphatase, total bilirubin
 - Cardiac evaluation for high risk individuals (e.g., potential for bradycardia, heart block, QTc prolongation, etc.)
 - Electrocardiogram
 - Where clinically indicated, spirometric evaluation of respiratory function
 - Ophthalmologic evaluation for macular edema risk (e.g., diabetes, uveitis)
 - Skin examination
 - Negative pregnancy test for women of childbearing age
 - Evidence of varicella zoster virus (VZV) immunity by **ONE** of the following:
 - A healthcare provider confirmed history of chickenpox
 - Documented full course of VZV vaccination
 - Positive antibodies to VZV; any needed vaccination of antibody negative patients to be completed 1 month before initiation
 - **For Mayzent:** Tested for CYP2C9 variants to determine genotype

Alternative Therapies

- **Mayzent and Ponvory:** Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, one is not a candidate for **at least ONE** of the following: [**Note:** Some of the following require prior authorization.]
 - Teriflunomide (Aubagio and generic)
 - Glatiramer acetate injection (Copaxone, Glatopa)
 - **ONE** interferon beta 1a or beta 1b injection (Avonex, Plegridy, Rebif, Betaseron, Extavia)
 - **ONE** fumarate product (Bafiertam, dimethyl fumarate, Vumerity)

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Dimethyl fumarate, generic
Fingolimod, generic
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MAVENCLAD (cladribine)
MAYZENT (siponimod)
PONVORY (ponesimod)
TASCENSO ODT (fingolimod lauryl sulfate)
TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Fingolimod (brand or generic)
 - Kesimpta (ofatumumab) injection
 - **Gilenya or Tascenso ODT or other generic fingolimod:** Individual has failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or is not a candidate for **generic fingolimod by CIVICASCRIP**T [Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **NONE** of the following:
 - Significant cardiovascular disease such as myocardial infarction, unstable angina, stroke, and transient ischemia attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure in the past 6 months
 - AV node block (ex., Mobitz type II 2nd degree or 3rd degree block), sick sinus syndrome, unless the individual has a pacemaker
 - Significant QTc interval prolongation (QTc greater than or equal to 500 msec)
 - Significant cardiac arrhythmias requiring treatment with Class IA or Class III antiarrhythmic drugs
 - Active infection
 - Macular edema or uveitis in an individual at risk (e.g., diabetes mellitus)
 - Non active secondary progressive multiple sclerosis
 - Concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy

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VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Significant interacting drugs
 - **For Mayzent, NONE** of the following:
 - CYP2C9*3/*3 genotype
 - New York Heart Association Class II, III, IV heart failure
 - **For Ponvory, NONE** of the following:
 - Moderate or severe hepatic impairment (Child Pugh Class B and C)
 - Resting heart rate of less than 50 bpm at baseline
 - History of syncope associated with cardiac disorders
 - Uncontrolled systemic arterial hypertension

Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes
 - Lab results (CBC, liver function, pregnancy test, varicella zoster antibody)
 - Electrocardiogram report
 - MRI report
 - Ophthalmologic evaluation report

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist

Clinical Response

- Achieves and maintains **TWO** of the following:
 - Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
 - Clinically stable neurologic exam
 - Reduction in number of exacerbations or relapses of MS
 - Prolonged time to exacerbation or relapses of MS
 - Reduction in use of high dose steroids or hospitalizations for MS

Adherence

- Adherence to the prescribed therapy regimen has been documented

Alternative Therapies

- **Gilenya or Tascenso ODT or other generic fingolimod:** Individual has failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance, or is not a candidate for **generic fingolimod by CIVICASCRIP** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new FDA label contraindications

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- No significant drug to drug interactions or adverse effects such as:
 - Severe, uncontrolled infection
 - Macular edema or uveitis
 - Serious arrhythmia such as symptomatic bradycardia, AV block, QT prolongation, etc.
 - Liver toxicity/injury
 - Posterior Reversible Encephalopathy Syndrome (PRES)
 - Progressive Multifocal Leukoencephalopathy (PML)
 - **NONE** of the following:
 - Significant cardiovascular disease such as myocardial infarction, unstable angina, stroke, and transient ischemia attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure in the past 6 months
 - AV node block (e.g., Mobitz type II 2nd degree or 3rd degree block), sick sinus syndrome, unless the individual has a pacemaker
 - Significant QTc interval prolongation (QTc greater than or equal to 500 msec)
 - Significant cardiac arrhythmias requiring treatment with Class IA or Class III antiarrhythmic drugs
 - Active infection
 - Macular edema or uveitis in an individual at risk (e.g., diabetes mellitus)
 - Non active secondary progressive multiple sclerosis
 - Concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
 - Significant interacting drugs
 - **For Mayzent, NONE** of the following:
 - CYP2C9*3/*3 genotype
 - New York Heart Association Class II, III, IV heart failure
 - **For Ponvory, NONE** of the following:

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Generic Equivalent (if available)

-
- Moderate or severe hepatic impairment (Child Pugh Class B and C)
 - Resting heart rate of less than 50 bpm at baseline
 - History of syncope associated with cardiac disorders
 - Uncontrolled systemic arterial hypertension

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use (CBC, liver function tests)
- Ophthalmologic evaluation if indicated

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year
- If criteria for response to therapy is not met, consider changing disease modifying therapy

Medical Necessity Requirements for **ZEPOSIA** (ozanimod)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist or Gastroenterologist

Indication

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Relapsing forms of multiple sclerosis (MS) including:
 - Relapsing remitting disease
 - Clinically isolated syndrome (CIS)
 - Active secondary progressive disease
 - Moderately to severely active ulcerative colitis (UC)

Age Requirement

- 18 years old

Baseline Clinical Evaluation

- **For MS, BOTH** of the following:
 - Clinical symptoms or attack consistent with demyelinating disease
 - MRI of the brain and/or spinal cord was performed and with **ONE** of the following:
 1. Magnetic resonance imaging [MRI] is consistent with the diagnosis of MS
 2. If an MRI is insufficient for the diagnosis of MS, a cerebrospinal fluid (CSF) evaluation was done and demonstrates CSF specific oligoclonal bands consistent with MS
- **For UC, BOTH** of the following:
 - Moderate to severe UC defined by the American College of Gastroenterology Ulcerative Colitis activity index rating of disease
 - Has at least five signs and symptoms ([see Definitions section](#))
- Complete blood count with differential within prior 6 months
- Liver function tests within prior 6 months: serum aminotransferase, alkaline phosphatase, total bilirubin
- Cardiac evaluation for high risk individuals (e.g., potential for bradycardia, heart block, QTc prolongation, etc.)
- Electrocardiogram

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- Where clinically indicated, spirometric evaluation of respiratory function
- Ophthalmologic evaluation for macular edema risk (e.g., diabetes, uveitis)
- Negative pregnancy test for women of childbearing age
- Evidence of varicella zoster virus (VZV) immunity by **ONE** of the following:
 - A healthcare provider confirmed history of chickenpox
 - Documented full course of VZV vaccination
 - Positive antibodies to VZV; any needed vaccination of antibody negative patients to be completed 1 month before initiation

Alternative Therapies

- For **MS**, **BOTH** of the following:
 - Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance to generic fingolimod
 - Documented failure after a trial of at least four (4) weeks, contraindication per FDA label, intolerance to **ONE** of the following: [**Note**: Some of the following require prior authorization.]
 1. Teriflunomide (Aubagio and generic)
 2. Glatiramer acetate injection (Copaxone, Glatopa)
 3. **ONE** interferon beta 1a or beta 1b injection (Avonex, Plegridy, Rebif, Betaseron, Extavia)
 4. **ONE** fumarate product (Bafiertam, dimethyl fumarate, Vumerity)
 5. Kesimpta (ofatumumab) injection
- For **UC**, **BOTH** of the following:
 - Failure (used for greater than 3 consecutive months), contraindication per FDA label, intolerance, or is not a candidate for **ONE** or more of the following: [**Note**: This criterion is waived if the individual already has tried an FDA approved Ulcerative Colitis biologic.]
 1. 6 mercaptopurine
 2. Azathioprine
 3. Oral corticosteroids
 4. Salicylates (such as mesalamine, sulfasalazine, balsalazide, olsalazine)

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Failure (used for greater than 3 consecutive months), contraindication per FDA label, intolerance to **TWO** or more of the following:
 1. Adalimumab product
 2. Rinvoq (upadacitinib)
 3. Skyrizi (risankizumab) (IV&SQ)
 4. Simponi (golimumab)
 5. Ustekinumab product
 6. Tremfya (guselkumab) (IV&SQ)
 7. Xeljanz or Xeljanz XR (tofacitinib)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications:
 - Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, Class III/IV heart failure
 - Severe untreated sleep apnea
 - Use of antiarrhythmic drugs that prolong QT interval
 - Pregnancy or lack of effective contraception
 - Active chronic infections
- No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
- **NONE** of the following:

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Generic Equivalent (if available)

-
- Significant cardiovascular disease such as myocardial infarction, unstable angina, stroke, and transient ischemia attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure in the past 6 months
 - AV node block (e.g., Mobitz type II 2nd degree or 3rd degree block), sick sinus syndrome, unless the individual has a pacemaker
 - Significant cardiac arrhythmias requiring treatment with Class IA or Class III anti arrhythmic drugs
 - Individual with an active infection
 - Macular edema or uveitis in an individual at risk (e.g., diabetes mellitus)
 - Severe untreated sleep apnea
 - Concomitant use a monoamine oxidase inhibitor (e.g., selegiline, phenelzine, linezolid)
 - Individual with non active secondary progressive multiple sclerosis
 - Requested treatment will not be used concurrently with other multiple sclerosis disease modifying therapy ([see Definitions section](#)) or other immunomodulatory, immunosuppressive, myelosuppressive therapy, or other biologics (e.g., Adalimumab product, Rinvoq, Simponi, Ustekinumab products, Xeljanz or /Xeljanz XR) for other conditions
 - Individual does not have severe hepatic impairment (Child Pugh Class C)
 - Individual does not have a resting heart rate of less than 55 bpm at baseline
 - Concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
 - Significant interacting drugs

Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes
 - Lab results (CBC, liver function, pregnancy test, varicella zoster antibody)
 - Electrocardiogram report
 - MRI report

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Ophthalmologic evaluation report

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist or Gastroenterologist

Clinical Response

- For **multiple sclerosis**, **TWO** of the following:
 - Mild/minimal to no functional neurologic (pyramidal, cerebellar, brainstem, sensory) disabilities
 - Clinically stable neurologic exam
 - Reduction in number of exacerbations or relapses of MS
 - Prolonged time to exacerbation or relapses of MS
 - Reduction in use of high dose steroids or hospitalizations for MS
- For **ulcerative colitis**, **TWO** of the following:
 - Achieved and maintains clinical remission or clinical response
 - Achieved and maintains endoscopic improvement or endoscopic histologic mucosal improvement
 - Achieved and maintains corticosteroid free clinical remission

Adherence

- Adherence to the prescribed therapy regimen has been documented

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Generic Equivalent (if available)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new FDA label contraindications
- No significant drug to drug interactions or adverse effects such as:
 - Severe, uncontrolled infection
 - Macular edema or uveitis
 - Serious arrhythmia such as symptomatic bradycardia, AV block, QT prolongation, etc.
 - Liver toxicity/injury
 - Posterior Reversible Encephalopathy Syndrome (PRES)
 - Progressive Multifocal Leukoencephalopathy (PML)
- **NONE** of the following:
 - Significant cardiovascular disease such as myocardial infarction, unstable angina, stroke, and transient ischemia attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure in the past 6 months
 - AV node block (e.g., Mobitz type II 2nd degree or 3rd degree block), sick sinus syndrome, unless the individual has a pacemaker
 - Significant QTc interval prolongation (QTc greater than or equal to 500 msec)
 - Significant cardiac arrhythmias requiring treatment with Class IA or Class III anti arrhythmic drugs
 - Active infection
 - Macular edema or uveitis in an individual at risk (e.g., diabetes mellitus)
 - Non active secondary progressive multiple sclerosis

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VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
 - Significant interacting drugs

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use (CBC, liver function tests)
- Ophthalmologic evaluation if indicated

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year
- If criteria for response to therapy is not met, consider changing disease modifying therapy

Medical Necessity Requirements for **AUBAGIO** (teriflunomide) and **Teriflunomide** generic

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist

Indication

- Relapsing forms of multiple sclerosis (MS) including:
 - Relapsing remitting disease

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TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Clinically isolated syndrome (CIS)
 - Active secondary progressive disease

Age Requirement

- 18 years old

Baseline Clinical Evaluation

- Clinical symptoms or attack consistent with demyelinating disease
- MRI of the brain and/or spinal cord was performed and with **ONE** of the following:
 - Magnetic resonance imaging [MRI] is consistent with the diagnosis of MS
 - If an MRI is insufficient for the diagnosis of MS, a cerebrospinal fluid (CSF) evaluation was done and demonstrates CSF specific oligoclonal bands consistent with MS
- Complete blood count with differential within prior 6 months
- Liver function tests within prior 6 months: serum aminotransferase, alkaline phosphatase, total bilirubin
- Screening for latent tuberculosis infection with a tuberculin skin test or blood test; if positive, treat tuberculosis with standard medical therapy before use of teriflunomide
- Blood pressure with treatment if needed
- Negative pregnancy test for women of childbearing age

Brand Specific Criteria

- For Aubagio (teriflunomide), failure, contraindication or intolerance with **THREE** equivalents of **generic teriflunomide** (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA label contraindications such as:

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PHARMACY COVERAGE GUIDELINE

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AUBAGIO (teriflunomide)
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Dalfampridine ER, generic
Dimethyl fumarate, generic
Fingolimod, generic
GILENYA (fingolimod)
MAVENCLAD (cladribine)
MAYZENT (siponimod)
PONVORY (ponesimod)
TASCENSO ODT (fingolimod lauryl sulfate)
TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Severe hepatic impairment (Child Pugh Class C)
 - Concurrent use with Arava (leflunomide)
 - History of a hypersensitivity reaction to teriflunomide (Aubagio or generic), Arava (leflunomide), or to any of the inactive ingredients in teriflunomide (Aubagio or generic)
 - Pregnancy or lack of effective contraception
 - No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
 - No live vaccines concurrently
 - No active acute or chronic infection

Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes
 - Lab results (CBC, liver function, pregnancy test)
 - MRI report

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist

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Generic Equivalent (if available)

Clinical Response

- Achieves and maintains **TWO** of the following:
 - Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
 - Clinically stable neurologic exam
 - Reduction in number of exacerbations or relapses of MS
 - Prolonged time to exacerbation or relapses of MS
 - Reduction in use of high dose steroids or hospitalizations for MS

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- For Aubagio (teriflunomide), failure, contraindication or intolerance with **THREE** equivalents of **generic teriflunomide** (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new FDA label contraindications or adverse effects such as:
 - Severe hepatic impairment (Child Pugh Class C)
 - Concurrent use with Arava (leflunomide)
 - History of a hypersensitivity reaction to teriflunomide (Aubagio or generic), Arava (leflunomide), or to any of the inactive ingredients in teriflunomide (Aubagio or generic)
 - Pregnancy or lack of effective contraception
 - Severe liver injury
 - Severe immunodeficiency

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Bone marrow depression
 - Severe peripheral neuropathy
 - Interstitial lung disease, including acute interstitial pneumonitis
 - Anaphylaxis, angioedema
 - Stevens Johnson syndrome
 - Toxic epidermal necrolysis
 - Drug reaction with eosinophilia and systemic symptoms (DRESS)
 - Pancreatitis
 - No concomitant use with other MS disease modifying therapy or other immunomodulatory, immunosuppressive, or myelosuppressive therapy
 - No live vaccines concurrently
 - No active acute or chronic infection

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use (CBC, liver function tests)

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year
- If criteria
- for response to therapy is not met, consider changing disease modifying therapy

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TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

Medical Necessity Requirements for **AMPYRA** (dalfampridine extended-release) and **Dalfampridine ER** generic

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a physician specializing in the diagnosis or in consultation with a Neurologist

Indication

- To improve walking in patients with multiple sclerosis (MS)

Age Requirement

- 18 years old

Baseline Clinical Evaluation

- Documented diagnosis of multiple sclerosis
- Ambulatory and **ONE** of the following:
 - Timed 25 foot walk test performed prior to initiation with speed of between 8 and 45 seconds
 - Significant limitations of instrumental activities of daily living attributable to slow ambulation
- Baseline creatinine clearance (CrCl) is greater than 50 mL/min

Brand Specific Criteria

- **For brand Ampyra (dalfampridine ER) or other generic dalfampridine ER:** Individual has failure after a 3 month trial, contraindication per FDA label, intolerance, or is not a candidate for **generic dalfampridine ER by CIVICASCRIP** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))

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TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

Safety

- No FDA label contraindications:
 - History of seizures
 - Moderate or severe renal impairment (creatinine clearance less than or equal to 50 mL per minute)
 - Hypersensitivity to Ampyra, dalfampridine, or 4 aminopyridine (4 AP, fampridine)
- Will not be used with Firdapse (amifampridine phosphate) or Ruzurgi (amifampridine)

Additional Requirements

- Will continue to use of disease modifying MS therapy agents
- Prescribed dosage will not be greater than 10mg twice daily

Documentation Requirements

- A completed request form must be submitted including:
 - Chart notes
 - Lab results (renal function, pregnancy test)
 - Timed 25 foot walk test results
 - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualification

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

- Continues to be seen by a physician specializing in the diagnosis or in consultation with a Neurologist

Clinical Response

- Condition has responded while on therapy with response defined as the following:
 - Improvement in walking speed of at least 20 percent over baseline
 - Remains ambulatory

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- **For brand Ampyra (dalfampridine ER) or other generic dalfampridine ER:** Individual has failure after a 3 month trial, contraindication per FDA label, intolerance, or is not a candidate for **generic dalfampridine ER by CIVICASCRIP** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] ([see Definitions section](#))

Safety

- No new FDA label contraindications or other significant adverse drug effects that may exclude continued use as follows:
 - History of seizures
 - Moderate or severe renal impairment (creatinine clearance less than or equal to 50 mL per minute)
 - Hypersensitivity to Ampyra, dalfampridine, or 4 aminopyridine (4 AP, fampridine)
- Will not be used with Firdapse (amifampridine phosphate) or Ruzurgi (amifampridine)

Additional Requirements

- Will continue to use of disease modifying MS therapy agents

Documentation Requirements

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Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

-
- Chart notes
 - Supporting clinical documentation with evidence of improvement
 - Lab values confirming safe use (renal function)
 - Timed 25 foot walk test results

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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 Non-Cancer Medications
2. Off-Label Use of Cancer Medications

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.

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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.

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Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

Mavenclad (cladribine) 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 (cladribine) 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 (cladribine) is not recommended for use in patients with CIS because of its safety profile.

Mavenclad (cladribine) 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 (cladribine) 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 (cladribine) more than 2 years after completing 2 treatment courses has not been studied.

Dimethyl fumarate (brand Tecfidera, and generic) 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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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

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.

Fingolimod (brand Gilenya, Tascenso ODT, and generic) 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 for the brand (18 years of age or older for the generic), to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. 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 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.

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ZEPOSIA (ozanimod)
Generic Equivalent (if available)

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.

Zeposia (ozanimod) is also indicated for the treatment of moderately to severely active ulcerative colitis.

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.

Dalfampridine (brand Ampyra and generic) is 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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
[MedWatch Forms for FDA Safety Reporting | FDA](#)

MS attack/exacerbation/relapse episode:

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Generic Equivalent (if available)

A monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or sub-acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonymous.

Pseudorelapse:

Temporary worsening of existing MS symptoms caused by increased body temperature, underlying infection, metabolic disturbance, or medical illness.

Stages or subtypes of Multiple Sclerosis:

- **Clinically Isolated Syndrome (CIS):**
CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system and is suggestive of MS. The episode, by definition must last for at least 24 hours, is characteristic of MS but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS. CIS symptoms develop over a course of hours to days and then decline over weeks to months and the remission may not be complete. CIS is an isolated attack in time (not necessarily isolated in space) and is a potential precursor to MS.
The diagnosis of MS can be made for some individuals at the time of presentation of a first clinical attack of CIS if a single MRI obtained at any time shows dissemination in space and evidence for dissemination in time showing simultaneous presence of gadolinium-enhancing and non-enhancing lesions, **or** (as a substitute for dissemination in time) by the presence of cerebrospinal fluid-specific oligoclonal bands.
- **Radiological Isolated Syndrome (RIS):**
RIS is defined by incidental MRI findings that are highly suggestive of MS, based upon location and morphology within the central nervous system, in an asymptomatic patient lacking any history, symptoms, or signs of demyelination. The MRI by definition was obtained for a completely unrelated condition.
- **Relapsing-Remitting (RRMS):**

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Generic Equivalent (if available)

RRMS is characterized by clearly defined attacks (relapses, flare-ups, or exacerbations), followed by full recover or with sequelae and residual deficit on recovery. There is no or minimal disease progression during periods between relapses. Individual relapses may result in severe residual disability. Approximately 85 percent of people with MS are initially diagnosed with RRMS and most will eventually enter a secondary progressive phase.

- **Secondary Progressive (SPMS):**
SPMS follows after the relapsing-remitting disease. Most individuals who are diagnosed with RRMS will eventually transition to SPMS in which there is a steady worsening of neurologic function (accumulation of disability) with or without superimposed attacks. At this stage, there is a reduction in relapse rate and new lesions are less common (so-called immunosenescence) but progressive (disability) MS increases. This type of MS causes the greatest amount of neurologic disability from MS.
- **Primary Progressive (PPMS):**
PPMS is characterized by disease progression (accumulation of disability) from the onset of symptoms, with occasional plateaus, temporary minor improvements; acute relapses may occur.
- **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.

Disease activity and progression:

- *Activity* is determined by clinical relapses or MRI evidence of contrast enhancing lesions and/or new or unequivocally enlarging T2 lesions
- *Progression* is a measure of disability, and it is independently quantified from relapses; it is characteristic of PPMS and SPMS
- Progressive disease (PPMS and SPMS) can be characterized as one of the following:
 - Active and with progression

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- Active without progression
- Not active but with progression
- Not active and without progression (stable disease)

Most Common Clinical Symptoms of MS attack (wide range of symptoms affecting different parts of the body):

- Unilateral optic neuritis (loss or reduction of vision in 1 eye with painful eye movements)
- Diplopia
- Ascending sensory disturbance and/or weakness
- Altered sensation or pain travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's sign)
- Progressive difficulties with balance and gait

McDonald criteria, 2017:

# Clinical attacks	# Lesions with objective clinical evidence	Additional data needed for a diagnosis of MS
2 or more	2 or more	None ^a
	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location ^b)	None ^a
	1	Dissemination in space demonstrated by an additional attack implicating a different CNS site by MRI
1	2 or more	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands ^c

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	1	<p>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI</p> <p>AND</p> <p>Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands^c</p>
<p>a: No additional tests are required to demonstrate dissemination in space and time; however, a brain MRI should be obtained in all individuals in whom a diagnosis of MS is being considered</p>		
<p>b: Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings.</p>		
<p>c: The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure</p>		
<p>Criteria for Dissemination in Space</p>		
<p>Dissemination in space is defined as the development of lesions in distinct anatomic locations within the central nervous system, indicating a multifocal process.</p> <p>The McDonald criteria for dissemination in space are fulfilled if one of the following is present in a patient with a CIS or typical MS attack:</p> <ul style="list-style-type: none"> • An MRI with <i>one or more hyperintense T2 lesions</i> that are <i>characteristic of MS</i> in at least two of four MS-typical regions of the central nervous system: <ul style="list-style-type: none"> ○ Periventricular ○ Cortical or juxtacortical ○ Infratentorial ○ Spinal cord • Development of an additional clinical attack characteristic of MS, supported by objective clinical evidence, that implicates a different central nervous system site 		

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Criteria for Dissemination in Time

Dissemination in time requires the development or appearance of new central nervous system lesions over time.

The McDonald criteria for dissemination in time are fulfilled if **one** of the following is present in a patient with a CIS or a characteristic MS attack:

- The development of an additional clinical attack, supported by objective clinical evidence, that is characteristic of MS
- An MRI of the brain and/or spinal cord with the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, or by a new hyperintense T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan
- Finding of cerebrospinal fluid-specific oligoclonal bands (as a substitute for dissemination in time)

Disease Modifying Therapy Options:

- Oral Medications:
 - Cladribine (Mavenclad)
 - Fumarates:
 - Dimethyl Fumarate (Tecfidera and generic)
 - Diroximel fumarate (Vumerity)
 - Monomethyl fumarate (Bafiertam)
 - Sphingosine-1-phosphate (S1P) receptor modulators
 - Fingolimod (Gilenya and generic, Tascenso ODT)
 - Ozanimod (Zeposia)
 - Ponesimod (Ponvory)
 - Siponimod (Mayzent)
 - Teriflunomide (Aubagio and generic)
- Injectable Medications:
 - Interferon beta-1a (Avonex (IM), Plegridy (SQ), Rebif (SQ))
 - Interferon beta-1b (Betaseron (SQ), Extavia (SQ))

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- Glatiramer acetate (Copaxone (SQ), and generic, Glatopa (SQ))
- Monoclonal antibody Mediations:
 - Alemtuzumab (Lemtrada IV)
 - Natalizumab (Tysabri IV)
 - Ocrelizumab (Ocrevus IV)
 - Ofatumumab (Kesimpta SQ)
 - Ublituximab (Briumvi IV)

Drug interactions Sphingosine-1-phosphate (S1P) receptor modulators:

Fingolimod	<ul style="list-style-type: none"> • Avoid the use of live attenuated vaccines during and for 2 months after treatment because of the risk of infection • Patients on QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility • Experience with fingolimod in patients receiving concurrent therapy with drugs that slow the heart rate or AV conduction (e.g., beta blockers, digoxin, or heart rate-slowing calcium channel blockers, such as diltiazem or verapamil) is limited. Seek advice from the physician prescribing these drugs regarding the possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction before initiating fingolimod. Patients who cannot switch should have overnight continuous ECG monitoring after the first dose • When switching from drugs with prolonged immune effects, such as natalizumab, teriflunomide or mitoxantrone, the duration and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects when initiating fingolimod
Ozanimod	<ul style="list-style-type: none"> • Live attenuated vaccines should be avoided during ozanimod treatment and for up to 3 months after discontinuation of treatment with ozanimod • Initiating treatment with ozanimod after alemtuzumab is not recommended because of the characteristics and duration of alemtuzumab immune suppressive effects • If treatment initiation with ozanimod is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought • Patients should be advised to avoid foods containing a large amount of tyramine while taking recommended doses of ozanimod

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	<ul style="list-style-type: none"> • Co-administration of ozanimod with MAO inhibitors (e.g., selegiline, phenelzine, linezolid) is contraindicated • Co-administration of ozanimod with strong CYP2C8 inhibitors (e.g., gemfibrozil, montelukast) is not recommended • Co-administration of ozanimod with strong CYP2C8 inducers (e.g., rifampicin) should be avoided
Ponesimod	<ul style="list-style-type: none"> • The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ponesimod treatment and for 1 to 2 weeks after discontinuation of treatment with ponesimod • Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with ponesimod after alemtuzumab is not recommended • Treatment with ponesimod should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., digoxin). If treatment with ponesimod is considered, advice from a cardiologist should be sought • Coadministration of ponesimod with strong CYP3A4 and UGT1A1 inducers is not recommended
Siponimod	<ul style="list-style-type: none"> • The use of live-attenuated vaccines may carry the risk of infection and should therefore be avoided during siponimod treatment and for up to 4 weeks after discontinuation of treatment with siponimod • Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with siponimod after alemtuzumab is not recommended • Treatment with siponimod should generally not be initiated in patients who are concurrently treated with QT prolonging drugs with known arrhythmogenic properties, heart rate lowering calcium channel blockers (e.g., verapamil, diltiazem), or other drugs that may decrease heart rate (e.g., ivabradine, digoxin) If treatment with siponimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation • Concomitant use of siponimod and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended • Concomitant use of siponimod and moderate (e.g., modafinil, efavirenz) or strong CYP3A4 inducers is not recommended for patients with CYP2C9*1/*3 or *2/*3 genotype

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:

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- 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)

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

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

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
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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

Signs and symptoms of Ulcerative Colitis:

- i. Anemia
- ii. Bloody diarrhea or visible blood in stool
- iii. Bowel movements 4-6 or more times per day
- iv. Colicky abdominal pain
- v. Elevated fecal calprotectin
- vi. Elevated serum C-reactive protein or erythrocyte sedimentation rate
- vii. Fatigue
- viii. Fever
- ix. Tenesmus
- x. Urgency

Ulcerative Colitis Activity:

American College of Gastroenterology Ulcerative Colitis Activity Index				
	Remission	Mild	Moderate-severe	Fulminant

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Stools (no./d)	Formed	< 4	> 6	> 10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	< 75% of normal	Transfusion needed
ESR	< 30	< 30	> 30	> 30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (mg/g)	< 150-200	> 150-200	> 150-200	> 150-200
Endoscopy (Mayo score)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8
The above factors are general guides for disease activity. With the exception of remission, a patient does not need to have all the factors to be considered in a specific category. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.				
Endoscopic Assessment of Disease Activity				
Endoscopic Features		UCEIS Score	Mayo Score	
Normal		0	0	
Erythema, decreased vascular pattern, mild friability		1-3	1	
Marked erythema, absent vascular pattern, friability, erosions		4-6	2	
Spontaneous bleeding, ulceration		7-8	3	

Resources:

Ampyra (dalfampridine) ER tab product information, revised by manufacturer Merz Pharmaceuticals, LLC. 03-2025, at DailyMed <http://dailymed.nlm.nih.gov>. Accessed January 29, 2026.

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TASCENSO ODT (fingolimod lauryl sulfate)
TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

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PHARMACY COVERAGE GUIDELINE

AMPYRA (dalfampridine ER)
AUBAGIO (teriflunomide)
BAFIERTAM (monomethyl fumarate)
Cladribine, generic
Dalfampridine ER, generic
Dimethyl fumarate, generic
Fingolimod, generic
GILENYA (fingolimod)
MAVENCLAD (cladribine)
MAYZENT (siponimod)
PONVORY (ponesimod)
TASCENSO ODT (fingolimod lauryl sulfate)
TECFIDERA (dimethyl fumarate)
Teriflunomide
VUMERITY (diroximel fumarate)
ZEPOSIA (ozanimod)
Generic Equivalent (if available)

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