Original Effective Date: 05/01/2019
Current Effective Date: 06/13/2024
Last P&T Approval/Version: 04/24/2024
Next Review Due By: 04/2025
Policy Number: C21142-A

Oral MS Disease-Modifying Therapies

PRODUCTS AFFECTED

Aubagio (teriflunomide), Bafiertam (monomethyl fumarate), dimethyl fumarate, fingolimod, Gilenya (fingolimod), Mavenclad (cladribine), Mayzent (siponimod), Ponvory (ponesimod), Tascenso ODT (fingolimod ODT), Tecfidera (dimethyl fumarate), teriflunomide, Vumerity (diroximel fumarate), Zeposia (ozanimod)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This 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 Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Multiple Sclerosis (MS), Ulcerative colitis (Zeposia only)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

Drug and Biologic Coverage Criteria

1. Documentation of a definitive diagnosis of a relapsing form of multiple sclerosis (MS) including: Relapsing-remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, and clinically isolated syndrome
   AND
2. Prescriber attests that member is not concurrently being treated with another MS disease modifying therapy (DMT) (See Appendix for list)
   AND
3. Documentation provided of drug specific pre-treatment assessment or planned assessment as recommended by each drug FDA label [**Aubagio:** transaminase and bilirubin levels, complete blood cell count (CBC), screen patients for latent tuberculosis infection, exclude pregnancy prior to initiation, and check blood pressure. **Bafiertam/Tecfidera/Vumerity:** CBC including lymphocyte counts, MRI, latent infection screening (e.g., hepatitis, tuberculosis) and liver function tests. **Gilenya/Tascenso:** CBC including lymphocyte counts, baseline bilirubin and transaminase levels, ECG, heart rate, blood pressure, and signs and symptoms of bradycardia, ophthalmologic exam, and evaluate pregnancy status, Vaccinate patients antibody negative to varicella zoster virus. **Mavenclad:** CBC including lymphocyte count, evaluate HIV, tuberculosis, hepatitis B (HBV) and hepatitis C (HCV) status, evaluate varicella zoster virus (VZV) antibody status, pregnancy test, liver function tests, MRI, and signs or symptoms of progressive multifocal leukoencephalopathy. **Mayzent:** CYP2C9 genotype testing, complete blood count (CBC), ophthalmic evaluation, cardiac evaluation, evaluate varicella zoster virus VZV antibody status, liver enzyme, skin examination, and Assess pulmonary function. **Ponvory:** CBC, including lymphocyte counts, Hepatic monitoring: Baseline bilirubin and transaminase levels, ECG (baseline); heart rate; BP; signs and symptoms of bradycardia, Ophthalmologic exam, respiratory function, Vaccinate patients antibody negative to varicella zoster virus, latent infection screening. **Zeposia:** CBC, including lymphocyte counts, Hepatic monitoring: Baseline bilirubin and transaminase levels, ECG (baseline); heart rate; BP; signs and symptoms of bradycardia, Ophthalmologic exam, respiratory function, Vaccinate patients antibody negative to varicella zoster virus, latent infection screening.]
   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [see individual contraindications in policy section - CONTRAINDICATIONS/EXCLUSIONS/ DISCONTINUATION]
   AND
5. FOR MAVENCLAD REQUESTS: Prescriber attests that Mavenclad (cladribine) is not being used to treat clinically isolated syndrome OR provides supportive documentation of medical necessity for treatment
   AND
6. FOR TASCENSO ODT REQUESTS: Documentation member is unable to ingest solid oral dosage form (i.e., capsule) due to ONE of the following: age, oral/motor difficulties, dysphagia
   AND
7. IF NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of inadequate response (6 months of therapy), serious side effects or FDA labeled contraindication to TWO preferred formulary disease modifying therapies. Inadequate response is defined as increase frequency, severity and/or sequelae of relapses, changes in MRI or increase in disability progression.
   AND
8. IF REQUEST IS FOR BRAND PRODUCT WITH GENERIC PREFERRED/FORMULARY (unless otherwise specified per applicable state regulations): Documentation the member has failed a trial of the respective generic product and/or the member cannot take the respective generic product due to a formulation difference in the active ingredient or due to a formulation difference in the inactive ingredient(s) [e.g., differences in dyes, fillers, preservatives between the brand and the generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician] [DOCUMENTATION REQUIRED]

B. ULCERATIVE COLITIS [ZEPOSIA (OZANIMOD) ONLY]:

1. Documentation of ulcerative colitis diagnosis with evidence of moderate to severe disease activity

AND

2. (a) Documentation of treatment failure, serious side effects or clinical contraindication to a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone) for ulcerative colitis or will continue to take concurrently.
   NOTE: A previous trial of a biologic (e.g., an adalimumab product [e.g., Humira], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion]) also counts as a trial of one systemic agent for UC.
   OR
   b) The Member has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema [for example, Cortenema® (hydrocortisone enema, generics)], or topical mesalamine
   AND
3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal
   AND
4. Documentation of a pre-treatment assessment or planned assessment as recommended by FDA label which includes: CBC, including lymphocyte counts; Hepatic monitoring: Baseline bilirubin and transaminase levels; ECG (baseline); heart rate; BP; signs and symptoms of bradycardia; Ophthalmologic exam; respiratory function evaluation; Vaccinate patients antibody negative to varicella zoster virus; and latent infection screening.
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review. [Contraindications to Zeposia (ozanimod) include: In the last 6 months, member has experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure; Presence of Mobitz type II second- degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker; Severe untreated sleep apnea; Concomitant use of a monoamine oxidase inhibitor.]
   AND
6. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

CONTINUATION OF THERAPY:

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response or stable disease based on ONE of the following:
   (a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
   OR
   (b) Documentation of lack of progression or sustained disability
   OR
   (c) Recent (within the last 6 months) MRI shows lack of development of new asymptomatic lesions
   AND
4. Prescriber attests to continued monitoring as required per drug specific FDA labeling

AND

5. FOR TASCENSO ODT REQUESTS: Documentation member is unable to ingest solid oral dosage form (i.e., capsule) due to ONE of the following: age, oral/motor difficulties, dysphagia

B. ULCERATIVE COLITIS [ZEPOSIA (OZANIMOD) ONLY]:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms
   AND
4. Prescriber attests to continued monitoring as required per FDA labeling

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
For the diagnosis of Multiple Sclerosis: Prescribed by, or in consultation with, a board-certified neurologist or a multiple sclerosis specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

For Zeposia (Ozanimod) requests for the diagnosis of ulcerative colitis: Prescribed by, or in consultation with, a board-certified gastroenterologist or colorectal surgeon. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
Gilenya: 10 years of age and older
Tascenso ODT: 10 years of age and older

ALL OTHER DMTS: 18 years of age and older

QUANTITY:
Aubagio (teriflunomide): 1 tablet per day

Bafiertam (monomethyl fumarate): 95 mg twice a day orally for 7 days. After 7 days, the dosage should be increased to the maintenance dosage of 190 mg (administered as two 95 mg capsules) twice a day orally. Maximum 4 capsules daily

Gilenya (fingolimod): Maximum dosage for 10 years or older OR more than 40 kg/88.2lbs: 0.5 mg orally once daily; Maximum dosage for ages 10 AND up to 40kg/88.2lbs: 0.25 mg orally once daily. If member exceeds 40kg/88.2lbs they will be recommended for the 0.5mg regardless of age.

Mavenclad (cladribine)
Quantity is limited to the exact number of tablets needed per body weight for each treatment course
40kg- <50kg: First Cycle- 40mg (4 tabs), Second Cycle- 40mg (4 tabs)
50kg- <60kg: First Cycle- 50mg (5 tabs), Second Cycle- 50mg (5 tabs)
60kg- <70kg: First Cycle- 60mg (6 tabs), Second Cycle- 60mg (6 tabs)
70kg- <80kg: First Cycle- 70mg (7 tabs), Second Cycle- 70mg (7 tabs)
80kg- <90kg: First Cycle- 80mg (8 tabs), Second Cycle- 70mg (7 tabs)
90kg- <100kg: First Cycle- 90mg (9 tabs), Second Cycle-8 0mg (8 tabs)

100g- <110kg: First Cycle- 100mg (10 tabs), Second Cycle- 90mg (9 tabs)
110kg and above: First Cycle- 100mg (10 tabs), Second Cycle- 100mg (10 tabs)

Mayzent (siponimod)
0.25mg tablets Starter Pack – blister card of twelve 0.25 mg tablets in a calendarized blister wallet - NDC 0078-0979-12. This starter pack is only intended for patients who will receive the 2 mg maintenance dosage. Patients with CYP2C9*1/*3 or *2/*3 genotype: maintenance max dose is 1mg once daily, all others maintenance max dose is 2mg once daily

Ponvory (ponesimod): Days 1,2 daily dose 2mg, Days 3,4 daily dose 3 mg, Days 5,6 daily dose 4mg, Day 7 daily dose 5mg, Day 8 daily dose 6mg, Day 9 daily dose 7mg, Day 10 daily dose 8 mg, Day 11 daily dose 9mg, Days 12,13,14 daily dose 10mg, Day 15 and after daily dose 20mg

Tascenso ODT (fingolimod): 10 years of age and older weighing less than or equal to 40 kg - 0.25 mg orally once daily; 10 years of age and older weighing more than 40 kg – 0.5 mg orally once daily

Tecfidera (dimethyl fumarate): Starting dose: 120 mg twice a day for 7 days, Maintenance dose after 7 days: 240mg twice daily

Vumerity (diroximel fumarate): Starting dose: 231 mg twice a day for 7 days, Maintenance dose after 7 days: 462 mg (administered as two 231 mg capsules) twice a day

Zeposia (ozanimod): Days 1-4 0.23 mg once daily Days 5-7 0.46 mg once daily Day 8 and thereafter 0.92 mg once daily; maximum of #1 0.92mg capsule per day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
MS Agents-Pyrimidine Synthesis Inhibitors
MS Agents-Antimetabolites
MS Agents-Nfr2 Pathway Activators
Sphingosine 1-Phosphate (S1P) Receptor Modulators

FDA-APPROVED USES:
Aubagio (teriflunomide) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Bafiertam (monomethyl fumarate) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Gilenya (fingolimod) indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older

Mavenclad (cladribine) Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety

profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.
Limitations of Use: Mavenclad is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

Mayzent (siponimod) indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Ponvory (ponesimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Tecfidera (dimethyl fumarate) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults

Tascenso ODT (fingolimod) indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in pediatric patients 10 years of age and older

Vumerity (diroximel fumarate) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Zeposia (ozanimod) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults and Moderately to severely active ulcerative colitis (UC) in adults.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Disease-modifying therapies for MS include: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), fingolimod (GilenyaTM), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocreliuzmab (OcrevusTM), siponimod (Mayzent®), Ponvory (ponesimod) and cladribine (Mavenclad®).
Summary of 2017 McDonald Criteria for the Diagnosis of MS

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by one of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by one of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by one of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord **AND** DIT shown by one of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least two of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time **CNS** = central nervous system **CSF** = cerebrospinal fluid
DIS = Dissemination in space **T2 lesion** = hyperintense lesion on T2-weighted MRI

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Multiple Sclerosis (MS)

MS is a chronic, inflammatory, autoimmune disease of the central nervous system that disrupts communications between the brain and other parts of the body. Most people experience their first symptoms of MS between the ages of 20 and 40 years of age. MS is among the most common causes of neurological disability in young adults and occurs more frequently in women than in men. MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Axonal injury is also a prominent pathologic feature, especially in the later stages. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms. For most people, MS starts with a relapsing-remitting course, in which episodes of worsening function (relapses) are followed by recovery periods (remissions). These remissions may not be complete and may leave patients with some degree of residual disability. Many, but not all, patients with MS experience some degree of persistent disability that gradually worsens over time. In some patients, disability may progress independent of relapses, a process termed secondary progressive multiple sclerosis (SPMS). In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as active SPMS. Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. On average, up to 80% of patients with relapsing- remitting (RRMS) – the most common form of MS at diagnosis – will develop SPMS. SPMS is a form of MS characterized by progressive and irreversible neurological disability. Most patients transition from RRMS to SPMS over time, which can vary if a patient is on disease modifying drug treatment or not.

RRMS – the most common disease course – is characterized by clearly defined attacks of new or increasing neurologic symptoms. These attacks – also called relapses or exacerbations – are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. At different points in time, RRMS can be further characterized as either active (with relapses and/or evidence of new MRI activity) or not active, as well as worsening (a confirmed increase in disability over a specified period of time following a relapse) or not worsening. An increase in disability is confirmed when the person exhibits the same level of disability at the next scheduled neurological evaluation, typically 6 to 12 months later.

Mayzent (siponimod)

The efficacy of Mayzent was demonstrated in the Phase III Expand study (Lancet, March 2018), a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry. My-MS.org9 Patients were randomized to receive either once daily Mayzent 2 mg or placebo, beginning with a dose titration. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected relapse. MRI evaluations were performed at screening and every 12 months. The primary endpoint of the study was the time to 3- month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A pre-specified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3- month confirmed worsening of at least 20% from baseline on the timed 25- foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate (relapses/year) and MRI measures of inflammatory disease activity. Study duration was variable for individual patients (median study duration was 21 months, range 1 day-37 months). EXPAND randomized 1651 patients to either Mayzent 2 mg (N = 1105) or placebo (N = 546); 82% of Mayzent treated patients and 78% of placebo- treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was

6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy. Mayzent was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio0.79, p < 0.0134; see Figure 1). Mayzent did not significantly delay the time to 20% deterioration in the timed 25- foot walk, compared to placebo.
Patients treated with Mayzent had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal pvalue < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although Mayzent had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of Mayzent inpatients with non- active SPMS was not statistically significant.

A total of 1737 MS patients have received Mayzent at doses of at least 2 mg daily. These patients were included in Phase III studies and in a Phase 2 placebo-controlled study in patients with MS. In Phase III Study 1, 67% of Mayzent treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of Mayzent treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in Mayzent treated patients were headache, hypertension, and transaminase increase.

Gilenya (fingolimod)
a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The recommended dose of Gilenya is 0.5 mg orally once daily. The initiation of Gilenya leads to decreases in heart rate. After the first dose of Gilenya, the heart rate decreases are noted within an hour and generally are greatest at 6 hours, although the effects can be observed 24 hours after the first dose in some patients. The first dose of Gilenya should be given in a setting with resources to appropriately manage symptomatic bradycardia.

Mavenclad (cladribine)
The efficacy of Mavenclad was shown in a clinical trial called CLARITY (Cladribine Tablets Treating Multiple Sclerosis Orally) which studied 1,326 patients with relapsing forms of MS who had least one relapse in the previous 12 months. The primary outcome of CLARITY was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium- enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in expanded disability status scale (EDSS) score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, at least 1.5points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months. Mavenclad 3.5 mg/kg resulted in a 58% relative reduction in annualized relapse rate over placebo, with 81% patients having no relapses compared to 63% placebo patients.
Per the FDA, Mavenclad must be dispensed with a patient Medication Guide that describes information about the drug's uses and risks. Mavenclad has a Boxed Warning for an increased risk of malignancy and fetal harm. Mavenclad should be stopped if the patient becomes pregnant.
Other warnings include the risk of decreased lymphocyte (white blood cell) counts; lymphocyte counts should be monitored before, during and after treatment. Mavenclad may increase the risk of infections; health care professionals should screen patients for infections, and treatment with Mavenclad should be delayed if necessary. Mavenclad may cause hematologic toxicity and bone marrow suppression, so health care professionals should measure a patient's complete blood counts before, during and after therapy. The drug has been associated with graft-versus-host- disease following blood transfusions with non- irradiated blood. Mavenclad may cause liver injury and treatment should be interrupted or discontinued, as appropriate, if clinically significant liver injury is suspected. The most common (>20%) adverse reactions reported by patients receiving Mavenclad include upper respiratory tract infection, headache, and decreased lymphocyte counts. Serious adverse reactions reported in the clinical

program included malignancies (0.27 events per 100 patient years) in Mavenclad treated arms, compared to placebo patients (0.13 events per 100 patient-years), herpes zoster infections (2.0% vs. 0.2%), and oral herpes (2.6% vs. 1.2%).

Tecfidera (dimethyl fumarate)
is indicated for the treatment of patients with relapsing forms of multiple sclerosis. The mechanism by which DMF exerts its therapeutic effect in multiple sclerosis 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.

Vumerity (diroximel fumarate)
The efficacy of Vumerity is based upon bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing Tecfidera to Vumerity. After oral administration of Vumerity, diroximel fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). Diroximel fumarate is not quantifiable in plasma following oral administration of Vumerity. Therefore, all pharmacokinetic analyses related to Vumerity were performed with plasma MMF concentrations. Pharmacokinetic data were obtained in subjects with relapsing forms of multiple sclerosis (MS) and healthy volunteers. All bioavailability studies met their endpoints. The key study for Biogen in providing differentiation from Tecfidera is the EVOLVE-MS-2 study. In July 2019, Biogen announced positive results from EVOLVE-MS-2, a randomized, double-blind, five-week, Phase 3study of diroximel fumarate compared to Tecfidera. According to the company's press release, diroximel fumarate was statistically superior to dimethyl fumarate on the study's pre-specified primary endpoint, with patients treated with diroximel fumarate self-reporting significantly fewer days of key gastrointestinal (GI) symptoms with intensity scores ≥2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS), as compared to dimethyl fumarate (p=0.0003). The most common adverse events (AEs) reported in the study for both treatment groups were flushing, diarrhea and nausea (32.8%, 15.4%, and 14.6% for diroximel fumarate; 40.6%, 22.3%, and 20.7% for dimethyl fumarate).
The overall proportion of patients with AEs leading to study discontinuation were 1.6% for diroximel fumarate and 6.0% for dimethyl fumarate. Of those, the proportion of patients who discontinued due to GI adverse events during the five-week treatment period were 0.8% for diroximel fumarate and 4.8% for dimethyl fumarate.

Zeposia (ozanimod)
The approval of Zeposia, a sphingosine 1-phosphate (S1P) receptor modulator, was based on data from2 double-blind, parallel-group, active comparator-controlled clinical trials in patients with relapsing forms of MS. Results showed that in both trials, the annualized relapse rate was statistically significantly lower in patients treated with Zeposia than in patients who received interferon beta-1a. With regard to safety, the most common adverse reactions reported included upper respiratory tract infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

The approval was based on efficacy data from the Phase 3 TEMSO (Teriflunomide Multiple Sclerosis Oral) trial evaluating more than 5,000 patients in 36 countries. Aubagio 14mg significantly reduced the annualized relapse rate (P=0.0005) and the time to disability progression (P=0.0279) at two years vs. placebo in patients with relapsing forms of MS. Additionally, Aubagio 7mg significantly reduced the annualized relapse rate (P=0.0002) in the trial.

Bafiertam (monomethyl fumarate)
Bafiertam is similar to Tecfidera® and Vumerity® but has a distinct chemical structure. Although their exact mechanisms of action are not known, fumarate therapies are thought to modulate the immune response underlying MS to be less inflammatory and may have antioxidant properties that could be

protective against damage to the brain and spinal cord.
Because of its similarity to Tecfidera, Bafiertam's approval was based largely on the FDA's findings of safety and efficacy for Tecfidera and "bioavailability" studies in healthy subjects comparing dimethyl fumarate to Bafiertam. Twice-daily Tecfidera was shown in clinical trials to significantly reduce relapses and disease activity on MRIs, and in one trial it reduced progression of disability.

Ponvory (ponseimod)
Ponesimod is a once-daily oral selective sphingosine-1-phosphate receptor 1 (S1P1) modulator.
The approval was based on results from a phase 3 head-to-head, randomized trial of ponesimod vs teriflunomide. A total of 1133 patients with relapsing MS, were randomly assigned to either ponesimod20mg once daily or teriflunomide 14mg once daily.
Results showed that the annualized relapse rate from baseline to Week 108 was reduced by 30.5%forthe ponesimod group vs the teriflunomide group, meeting the trial's primary endpoint. The Company stated that 71% of patients treated with ponesimod had no confirmed relapses, compared to 61% in the teriflunomide group.
Moreover, ponesimod showed superiority in reducing the number of new gadolinium- enhancing (GdE) T1 and T2 lesions compared with teriflunomide by 59% and 56%, respectively. As for adverse events, overall rates were similar to teriflunomide. The most common adverse events observed in the phase 3 trial in ponesimod-treated patients were upper respiratory infection, hepatic transaminase elevation, and hypertension.

Aubagio (teriflunomide)
Aubagio is a once-daily oral therapy approved in 2012 for relapsing MS, with a unique pyrimidine synthesis inhibitor mechanism of action. Four randomized, controlled, double-blind clinical trials established the efficacy of AUBAGIO in patients with relapsing forms of multiple sclerosis. Study 1 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of AUBAGIO 7 mg and AUBAGIO 14 mg for up to 26 months. There was a statistically significant reduction in ARR for patients who received AUBAGIO 7 mg or AUBAGIO 14 mg, compared to patients who received placebo. The effect of AUBAGIO on several magnetic resonance imaging (MRI) variables, including the total lesion volume of T2 and hypointense T1 lesions, was assessed in Study 1. The change in total lesion volume from baseline was significantly lower in the AUBAGIO 7 mg and AUBAGIO 14 mg groups than in the placebo group. Patients in both AUBAGIO groups had significantly fewer gadolinium-enhancing lesions per T1-weighted scan than those in the placebo group. Study 2 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of AUBAGIO 7 mg and AUBAGIO 14 mg for up to 40 months. There was a statistically significant reduction in the ARR for patients who received AUBAGIO 7 mg or AUBAGIO 14 mg compared to patients who received placebo. Study 3 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of AUBAGIO 7 mg and AUBAGIO 14 mg for up to 108 weeks in patients with relapsing multiple sclerosis. The proportion of patients free of relapse was greater in the AUBAGIO 7 mg (70.5%, $p<0.05$) and AUBAGIO 14mg (72.2%, $p<0.05$) groups than in the placebo group (61.7%). The effect of AUBAGIO on MRI activity was also demonstrated in Study 4, a randomized, double-blind, placebo-controlled clinical trial of multiple sclerosis patients with relapse. In Study 4, MRI was to be performed at baseline, 6 weeks, 12 weeks, 18 weeks, 24 weeks, 30 weeks, and 36 weeks after treatment initiation. A total of 179 patients were randomized. The mean number of unique active lesions per brain MRI scan during the 36-week treatment period was lower in patients treated with AUBAGIO 7 mg (1.06) and AUBAGIO 14 mg (0.98) as compared to placebo (2.69), the difference being statistically significant for both ($p=0.0234$ and $p=0.0052$, respectively).

<u>Progressive multifocal leukoencephalopathy</u>
Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in MAYZENT-treated patients in the development program; however, PML has been reported in patients treated with an S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). If PML is suspected, treatment with MAYZENT should be suspended until PML has been excluded.

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with parenteral cladribine for oncologic indications, cases of PML have been reported in the postmarketing setting. At the first sign or symptom suggestive of PML, withhold MAVENCLAD and perform an appropriate diagnostic evaluation.

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with MS who received fingolimod in the postmarketing setting. At the first sign or symptom suggestive of PML, withhold fingolimod and perform an appropriate diagnostic evaluation.

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with dimethyl fumarate (TECFIDERA; which has the same active metabolite as VUMERITY; the prodrug of BAFIERTAM). At the first sign or symptom suggestive of PML, withhold TECFIDERA, VUMERITY, BAFIERTAM and perform an appropriate diagnostic evaluation.

PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other multiple sclerosis (MS) and UC therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). If PML is suspected, treatment with ZEPOSIA should be suspended until PML has been excluded by an appropriate diagnostic evaluation. If PML is confirmed, treatment with ZEPOSIA should be discontinued.

PML has been reported in patients treated with a S1P receptor modulator and other multiple sclerosis (MS) therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). If PML is suspected, treatment with PONVORY should be suspended until PML has been excluded. If PML is confirmed, treatment with PONVORY should be discontinued.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of oral disease-modifying therapies are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.

Contraindications to Aubagio (teriflunomide) include: Patients with severe hepatic impairment, Pregnant women and females of reproductive potential not using effective contraception (Aubagio may cause fetal harm), Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in Aubagio, Coadministration with leflunomide.

Contraindications to Bafiertam (monomethyl fumarate) include: Known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or any of the excipients of Bafiertam, co-administration with dimethyl fumarate or diroximel fumarate.

Contraindications to Gilenya (fingolimod) and Tascenso ODT (fingolimod) include: Recent myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure with hospitalization, or Class III/IV heart failure, History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker, Baseline QTc interval ≥ 500 msec, Cardiac arrhythmias requiring anti- arrhythmic treatment with Class Ia or Class III anti- arrhythmic drugs, Hypersensitivity to fingolimod or its excipients.

Contraindications to Mavenclad (cladribine) include: Patients with current malignancy, Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course, HIV infection, Active chronic infections (e.g., hepatitis or tuberculosis), History of hypersensitivity to cladribine, Women intending to breastfeed on a Mavenclad treatment day and for 10 days after the last dose.

Contraindications to Mayzent (siponimod) include: Patients with a CYP2C9*3/*3 genotype, Myocardial

infarction within the last 6 months, Unstable angina within the last 6 months, Stroke or TIA within the last 6 months, Decompensated heart failure requiring hospitalization within the last 6 months, Class III or IV heart failure within the last 6 months, Mobitz type II second-degree or third-degree atrioventricular block, unless patient has a functional pacemaker and Sick-sinus syndrome, unless patient has a functional pacemaker.

Contraindications to Ponvory (ponesimod) include: In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure; Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker.

Contraindications to Tecfidera (dimethyl fumarate) include known hypersensitivity to dimethyl fumarate or any of the excipients of Tecfidera.

Contraindications to Vumerity (diroximel fumarate) include: Known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of Vumerity, Co- administration with dimethyl fumarate.

Contraindications to Zeposia (ozanimod) include: In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure, Presence of Mobitz type II second- degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker, Severe untreated sleep apnea, Concomitant use of a monoamine oxidase inhibitor.

OTHER SPECIAL CONSIDERATIONS:

Aubagio (teriflunomide) has a black box warning for hepatotoxicity and embryofetal toxicity.
Mavenclad (cladribine) has a black box warning for malignancies and risk of teratogenicity.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Aubagio TABS 14MG
Aubagio TABS 7MG
Bafiertam CPDR 95MG
Dimethyl Fumarate CPDR 120MG
Dimethyl Fumarate CPDR 240MG
Dimethyl Fumarate Starter Pack CDPK 120 & 240MG
Fingolimod HCl CAPS 0.5MG
Gilenya CAPS 0.25MG
Gilenya CAPS 0.5MG
Mavenclad (10 Tabs) TBPK 10MG
Mavenclad (4 Tabs) TBPK 10MG
Mavenclad (5 Tabs) TBPK 10MG
Mavenclad (6 Tabs) TBPK 10MG
Mavenclad (7 Tabs) TBPK 10MG
Mavenclad (8 Tabs) TBPK 10MG
Mavenclad (9 Tabs) TBPK 10MG

Mayzent Starter Pack TBPK 7 x 0.25MG
Mayzent Starter Pack TBPK 12 x 0.25MG
Mayzent TABS 0.25MG
Mayzent TABS 1MG
Mayzent TABS 2MG
Ponvory Starter Pack TBPK 2-3-4-5-6-7-8-9& 10 MG
Ponvory TABS 20MG
Tascenso ODT TBDP 0.25MG
Tascenso ODT TBDP 0.5MG
Tecfidera CPDR 120MG
Tecfidera CPDR 240MG
Tecfidera CDPK 120 & 240MG
Teriflunomide TABS 7MG
Teriflunomide TABS 14MG
Vumerity (Starter) CPDR 231MG
Vumerity CPDR 231MG
Zeposia 7-Day Starter Pack CPPK 4 x 0.23MG &3 x 0.46MG
Zeposia CAPS 0.92MG
Zeposia Starter Kit CPPK 0.23MG & 0.46MG& 0.92MG

REFERENCES

1. Ponvory (ponesimod) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; August 2023.
2. Mavenclad (cladribine) [prescribing information]. Rockland, MA: EMD Serono Inc; February 2024.
3. Tecfidera (dimethyl fumarate) [prescribing information]. Cambridge, MA: Biogen Idec Inc; December 2023.
4. Vumerity (diroximel fumarate) [prescribing information]. Cambridge, MA: Biogen Inc; December 2023.
5. Aubagio (teriflunomide) [prescribing information]. Cambridge, MA: Genzyme Corporation; December 2023.
6. Mayzent (siponimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2023.
7. Gilenya (fingolimod) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2023.
8. Tascenso ODT (fingolimod) orally disintegrating tablet [prescribing information]. Cambridge, UK: Handa Neuroscience, LLC; August 2023.
9. Bafiertam (monomethyl fumarate) [prescribing information]. High Point, NC: Banner Life Sciences LLC; December 2023.
10. Zeposia (ozanimod) [prescribing information]. Summit, NJ: Celgene Corporation; August 2023.
11. Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology. 2018;90(20): e1815-e1821. doi: 10.1212/WNL.0000000000005529.
12. Kappos L, Bar-Or A, Cree BAC, et al: Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 391(10127):1263-1273.
13. Gardin A, Gray C, Neelakantham S, et al: Siponimod pharmacokinetics, safety, and tolerability in combination with rifampin, a CYP2C9/3A4 inducer, in healthy subjects. Eur J Clin Pharmacol 2018; 74(12):1593-1604.
14. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology [published correction appears in Neurology. 2019;92(2):112]. Neurology. 2018;90(17):777- 788. [PubMed 29686116]10.1212/WNL.0000000000005347

15. O'Connor P, Wolinsky JS, Confavreux C, et al, for the TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011;365(14):1293-1303.
16. Freedman MS, Wolinsky JS, Wamil B, et al. Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. Neurology. Jun 5 2012;78(23):1877-1885.
17. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Available at: https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/WNL/A/WNL_2018_04_19_RAEGRANT_NEUROLOGY2017835181R1_SDC3.pdf. Published April 2018.
18. Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., & Sørensen, P. et al. (2010). A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. New England Journal Of Medicine, 362(5), 416-426. doi: 10.1056/nejmoa0902533
19. A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) - Full Text View - ClinicalTrials.gov. (2019). Retrieved from https://clinicaltrials.gov/ct2/show/NCT00213135

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Background Available Dosage Forms References	Q2 2024
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Age Restrictions FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Age Restrictions Quantity FDA-Approved Uses	Q4 2022
REVISION- Notable revisions: Required Medical Information Drug Class References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file