09-J5000-44

Original Effective Date: 03/15/26

Reviewed: 02/11/26

Revised: 00/00/00

Subject: Multiple Sclerosis: Oral and Self Injectable Therapy

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by triad of inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. MS has been categorized into four types: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS. Although a cure for MS remains elusive, several treatment options slow the progression of the disease and reduce the frequency of relapses.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, and Zeposia are the preferred brand products for treatment of relapsing forms of multiple sclerosis. The preferred generic products include dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by

Mylan), and teriflunomide (generic). Dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), and teriflunomide (generic) do not require prior authorization.

Initiation of the requested agent **meets the definition of medical necessity** when **ALL** of the following criteria are met:

a. Member is diagnosed with **ONE** of the following forms of multiple sclerosis (MS):
    a. Relapsing-remitting MS [RRMS]
    b. Active secondary-progressive MS [SPMS]
    c. First clinical episode and member has MRI features consistent with multiple sclerosis (MS) (*does not include cladribine*)
b. The requested agent will not be used in combination with an alternative agent FDA approved for the treatment of RRMS, active SPMS, or clinically isolated syndrome
c. Member meets drug specific initiation criteria in Table 1

Table 1. MS Oral and Self Injectable Initiation of Therapy	
Avonex	The dosage does not exceed 30 mcg intramuscularly weekly
Betaseron	The dosage does not exceed 0.3 mg subcutaneously every other day
Bafiertam	**ALL** of the following**:** 1. **BOTH** of the following ("a" and "b"): a. The member has tried and had intolerable adverse effects to generic dimethyl fumarate and **ALL** of the following must be submitted: i. The specific intolerance(s) to generic dimethyl fumarate and rationale for using Bafiertam must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b. **ONE** of the following ("I", "ii", or "iii") – documentation must be submitted: i. The patient has highly active MS disease activity and **BOTH** of the following: 1. The patient has ≥ 2 relapses in the previous year 2. **ONE** of the following: a. The patient has ≥ 1 gadolinium enhancing lesion on MRI

	b. The patient has significant increase in T2 lesion load compared with a previous MRI ii. The patient has been treated with at least 3 MS agents from different drug classes iii. **ONE** of the following ("1", "2", or "3"): 1. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to **ALL** preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The dose does not exceed 190 mg twice a day (max 380 mg daily)
Brand Aubagio	**ALL** of the following: a. The member has tried and had intolerable adverse effects to generic teriflunomide and **ALL** of the following must be submitted: i. The specific intolerance(s) and rationale for using brand Aubagio must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b. **ONE** of the following (i, ii, or iii) – documentation must be submitted: i. The patient has highly active MS disease activity and **BOTH** of the following: 1. The patient has ≥ 2 relapses in the previous year 2. **ONE** of the following: a. The patient has ≥ 1 gadolinium enhancing lesion on MRI b. The patient has significant increase in T2 lesion load compared with a previous MRI ii. The patient has been treated with at least 3 MS agents from different drug classes iii. **ONE** of the following (1, 2, or 3):

	1. The patient has tried and had an inadequate response to ONE preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) c. The member does not have severe hepatic impairment (Child-Pugh Class C) d. The dose does not exceed 14 mg daily
Brand Gilenya	**ALL** of the following: a. The member has tried and had intolerable adverse effects to generic fingolimod and **ALL** of the following must be submitted: i. The specific intolerance(s) and rationale for using brand Gilenya must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b. **ONE** of the following (i, ii, or iii) – documentation must be submitted: i. The patient has highly active MS disease activity and **BOTH** of the following: a. The patient has ≥ 2 relapses in the previous year b. **ONE** of the following: i. The patient has ≥ 1 gadolinium enhancing lesion on MRI ii. The patient has significant increase in T2 lesion load compared with a previous MRI ii. The patient has been treated with at least 3 MS agents from different drug classes iii. **ONE** of the following (a, b, or c): a. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) b. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or

	hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) c. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) c. The member does not have any of the following: i. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure ii. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker) iii. Prolonged QT interval (i.e., QTc > 500 ms) iv. Concomitant therapy with a Class Ia (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol, dofetilide) anti-arrhythmic drug d. The dosage does not exceed **ONE** of the following: i. 0.25 mg daily for a member 40 kg or less ii. 0.5 mg daily using the fewest capsules per day for a member more than 40 kg
Brand Tecfidera	**ALL** of the following: 1. **1.BOTH** of the following ("a" and "b"): b. The member has tried and had intolerable adverse effects to generic dimethyl fumarate and **ALL** of the following must be submitted: i. The specific intolerance(s) to generic dimethyl fumarate and rationale for using brand Tecfidera must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf c. **ONE** of the following ("I", "ii", or "iii") – documentation must be submitted: i. The patient has highly active MS disease activity and **BOTH** of the following: 1. The patient has ≥ 2 relapses in the previous year 2. **ONE** of the following: a. The patient has ≥ 1 gadolinium enhancing lesion on MRI

	b. The patient has significant increase in T2 lesion load compared with a previous MRI ii. The patient has been treated with at least 3 MS agents from different drug classes iii. **ONE** of the following ("1", "2',or "3"): 1. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to **ALL** preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The dose does not exceed 240 mg twice a day (max 480 mg daily)
Copaxone	**ALL** of the following: 1. The member has tried and had intolerable adverse effects to glatiramer acetate (by Mylan) and Glatopa and **ALL** of the following must be submitted: a. The specific intolerance(s) and rationale for using brand Copaxone must be specified b. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda c. Completed Naranjo Adverse Drug reaction probability scale - https://www.floridablue.com/docview/Naranjo-assessment-PDF/ 2. **ONE** of the following (a,b,or c) – documentation must be submitted: a. The patient has highly active MS disease activity and **BOTH** of the following: i. The patient has ≥ 2 relapses in the previous year ii. **ONE** of the following: 1. The patient has ≥ 1 gadolinium enhancing lesion on MRI 2. The patient has significant increase in T2 lesion load compared with a previous MRI b. The patient has been treated with at least 3 MS agents from different drug classes c. **ONE** of the following (i, ii, or iii):

	i. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) ii. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) iii. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The dosage does not exceed the following: a. Copaxone 20 mg: 20 mg subcutaneously daily b. Copaxone 40 mg: 40 mg subcutaneously three times a week
Extavia	**ALL** of the following: 1. **ONE** of the following (a,b,or c) – documentation must be submitted: a. The patient has highly active MS disease activity and **BOTH** of the following: i. The patient has ≥ 2 relapses in the previous year ii. **ONE** of the following: 1. The patient has ≥ 1 gadolinium enhancing lesion on MRI 2. The patient has significant increase in T2 lesion load compared with a previous MRI b. The patient has been treated with at least 3 MS agents from different drug classes c. **BOTH** of the following (i and ii): i. **ONE** of the following (1,2,or 3): 1. The patient has tried and had an inadequate response to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic) 3. The patient has a FDA labeled contraindication to both dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **AND** teriflunomide (generic)

	ii. **ONE** of the following (1,2,or 3): 1. The patient has tried and had an inadequate response to ONE preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The dosage does not exceed 0.3 mg subcutaneously every other day
Kesimpta	**ALL** of the following: 1. The member does not have an active Hepatitis B viral (HBV) infection 2. The initial dosage does not exceed 20 mg subcutaneously at week 0, 1, and 2, followed by 20 mg every 4 weeks starting at week 4
Mavenclad	**ALL** of the following**:** 1. Member has no evidence of current malignancy 2. Member will receive varicella zoster vaccine at least 4 weeks prior to the start of cladribine if the member is antibody-negative for varicella zoster virus 3. Member has tested negative for **ALL** of the following: a. Hepatitis B and C b. Tuberculosis c. HIV infection d. Pregnancy (only for women of reproductive potential) 4. The dose does not exceed weight based dosing in Table 3 for cycle 1 and 2 of the first treatment course. The first cycle is administered as one or 2 tablets over 4 to 5 days and the second cycle is administered as one or 2 tablets over 4 to 5 days that is provided 23 to 27 days after the last dose of the first cycle.
Mayzent	**ALL** of the following: 1. Member will receive varicella zoster vaccine at least 4 weeks prior to the start of simponimod if the member is antibody-negative for varicella zoster virus 2. Member does not have any of the following: a. CYP2C9*3/*3 genotype b. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure

	c. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker) 3. The dose does not exceed the following: a. CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: 2 mg daily using the fewest number of tablets per day b. CYP2C9*1/*3 or *2/*3 genotype: 1 mg daily using the fewest number of tablets per day
Plegridy	The dosage does not exceed 125 mcg every 14 days
Ponvory	**ALL** of the following: 1. **ONE** of the following (a,b,or c) – documentation must be submitted: a. The patient has highly active MS disease activity and **BOTH** of the following: i. The patient has ≥ 2 relapses in the previous year ii. **ONE** of the following: 1. The patient has ≥ 1 gadolinium enhancing lesion on MRI 2. The patient has significant increase in T2 lesion load compared with a previous MRI b. The patient has been treated with at least 3 MS agents from different drug classes c. **BOTH** of the following (i and ii): i. **ONE** of the following (1,2,or 3): 1. The patient has tried and had an inadequate response to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic) 3. The patient has a FDA labeled contraindication to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **AND** teriflunomide (generic) ii. **ONE** of the following (1,2,or 3): 1. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration)

	or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The member does not have any of the following: a. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure b. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker) c. Moderate or severe hepatic impairment (Child-Pugh class B or C) 3. The dosage does not exceed 20 mg daily
Rebif	The dosage does not exceed 44 mcg subcutaneously 3 times a week
Tascenso ODT	**ALL** of the following: 1. **ONE** of the following (a or b) – documentation must be submitted: a. The member is 18 year of age or older and **BOTH** of the following (i and ii): i. The member has tried and had intolerable adverse effects to generic fingolimod and **ALL** of the following must be submitted: 1. The specific intolerance(s) and rationale for using Tascenso ODT must be specified 2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda 3. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf ii. **ONE** of the following (1, 2, or 3): 1. The patient has highly active MS disease activity and **BOTH** of the following: a. The patient has ≥ 2 relapses in the previous year b. **ONE** of the following: i. The patient has ≥ 1 gadolinium enhancing lesion on MRI

	ii. The patient has significant increase in T2 lesion load compared with a previous MRI 2. The patient has been treated with at least 3 MS agents from different drug classes 3. **ONE** of the following (a,b,or c): a. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) b. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) c. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) b. The member is 17 years of age or younger and **ONE** of the following (1, 2, or 3): 1. The patient has highly active MS disease activity and **BOTH** of the following: a. The patient has ≥ 2 relapses in the previous year b. **ONE** of the following: i. The patient has ≥ 1 gadolinium enhancing lesion on MRI ii. The patient has significant increase in T2 lesion load compared with a previous MRI 2. The patient has been treated with at least 3 MS agents from different drug classes 3. **ONE** of the following (a,b, c, or d): a. The request is for Tascenso ODT 0.25 mg for a member 40 kg or less b. The patient has tried and had an inadequate response to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic) c. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic)

	d. The patient has a FDA labeled contraindication to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **AND** teriflunomide (generic) 2. The member does not have any of the following: a. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure b. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker) c. Prolonged QT interval (i.e., QTc > 500 ms) d. Concomitant therapy with a Class Ia (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol, dofetilide) anti-arrhythmic drug 3. The dose does not exceed **ONE** of the following: a. 0.25 mg daily for a member 40 kg or less b. 0.5 mg daily using the fewest tablets per day for a member more than 40 kg
Vumerity	**ALL** of the following: 1. **BOTH** of the following ("a" and "b"): a. The member has tried and had intolerable adverse effects to generic dimethyl fumarate and **ALL** of the following must be submitted: i. The specific intolerance(s) to generic dimethyl fumarate and rationale for using Vumerity must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b.**ONE** of the following ("I", "ii", or "iii") – documentation must be submitted: i. The patient has highly active MS disease activity and **BOTH** of the following: 1. The patient has ≥ 2 relapses in the previous year 2. **ONE** of the following: a. The patient has ≥ 1 gadolinium enhancing lesion on MRI

	b. The patient has significant increase in T2 lesion load compared with a previous MRI ii. The patient has been treated with at least 3 MS agents from different drug classes iii. **ONE** of the following ("1" ,"2" ,or '3'): 1. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 3. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia) 2. The dose does not exceed 462 mg twice a day (max 924 mg daily)
Approval duration: 1 year, for Mavenclad 9 months (One course of two 4 to 5 day treatment cycles)]	

Continuation of the requested agent **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has demonstrated a beneficial response to therapy for treatment of RRMS, active SPMS, or clinically isolated syndrome
2. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member currently meets all indication-specific initiation criteria
3. The requested agent will not be used in combination with an alternative agent FDA approved for the treatment of RRMS, active SPMS, or clinically isolated syndrome
4. Member meets drug specific continuation criteria in Table 2

Table 2. MS Oral and Self Injectable Continuation of Therapy	
Avonex	The dosage does not exceed 30 mcg intramuscular weekly
Betaseron	The dosage does not exceed 0.3 mg subcutaneous every other day
Bafiertam	The dose does not exceed 190 mg twice a day (max 380 mg daily)

Brand Aubagio	**ALL** of the following: a. The member has tried and had intolerable adverse effects to generic teriflunomide and **ALL** of the following must be submitted: i. The specific intolerance(s) and rationale for using brand Aubagio must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b. The dose does not exceed 14 mg daily
Brand Gilenya	**ALL** of the following: a.The member has tried and had intolerable adverse effects to generic fingolimod and ALL of the following must be submitted: i. The specific intolerance(s) and rationale for using brand Gilenya must be specified ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda iii. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf b.The dose does not exceed **ONE** of the following: i. 0.25 mg daily for a member 40 kg or less ii. 0.5 mg daily using the fewest capsules per day for a member more than 40 kg
Brand Tecfidera	**ALL** of the following: **1.** The member has tried and had intolerable adverse effects to generic dimethyl fumarate and **ALL** of the following must be submitted: a. The specific intolerance(s) and rationale for using brand Tecfidera must be specified b. Completed Medwatch reporting form (FDA 3500) – https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

	c. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf 2. The dose does not exceed 240 mg twice a day (max 480 mg daily)
Copaxone	**ALL** of the following: 1. The member has tried and had intolerable adverse effects to glatiramer acetate (by Mylan) and Glatopa and **ALL** of the following must be submitted: a.The specific intolerance(s) and rationale for using brand Copaxone must be specified b.Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda c.Completed Naranjo Adverse Drug reaction probability scale - https://www.floridablue.com/docview/Naranjo-assessment-PDF/ 2. The dose does not exceed the following: a.Copaxone 20 mg: 20 mg subcutaneously daily b.Copaxone 40 mg: 40 mg subcutaneously three times a week
Extavia	The dose does not exceed 0.3 mg subcutaneously every other day
Kesimpta	The dose does not exceed 20 mg subcutaneously every 4 weeks
Mavenclad (cladribine)	**ALL** of the following: 1. Member has not utilized an FDA-approved product for the treatment of RRMS or SPMS since initiating treatment with cladribine 2. Member has no evidence of current malignancy 3. Member has tested negative for **ALL** of the following: a. Hepatitis B and C b. Tuberculosis c. HIV infection d. Pregnancy (only for women of reproductive potential) 4. Member has a lymphocyte count of at least 800 cells/mL 5. Member has received less than a cumulative dose of 3.5 mg/kg of cladribine in their lifetime 6. Member completed the first course (consisting of the first course, cycle 1 and cycle 2) of cladribine at least 43 weeks prior to beginning the second treatment course (consisting of the second course, cycle 1 and cycle 2)

	7. The dose does not exceed weight based dosing in Table 3 for cycle 1 and 2 of the second treatment course. The first cycle is administered over 4 to 5 days and the second cycle is provided 23 to 27 days after the last dose of the first cycle.
Mayzent	The dose does not exceed the following: a. CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: 2 mg daily using the fewest number of tablets per day b. CYP2C9*1/*3 or *2/*3 genotype: 1 mg daily using the fewest number of tablets per day
Plegridy	The dosage does not exceed 125 mcg every 14 days
Ponvory	The dose does not exceed 20 mg daily
Rebif	The dosage does not exceed 44 mcg subcutaneous 3 times a week
Tascenso ODT	The dose does not exceed **ONE** of the following: a. 0.25 mg daily for a member 40 kg or less b. 0.5 mg daily using the fewest tablets per day for a member more than 40 kg
Vumerity	The dose does not exceed 462 mg twice a day (max 924 mg daily)
Approval duration: 1 year [Mavenclad approved for 3 months (One course of two 4 to 5 day treatment cycles)]	

Table 3. Dose of Mavenclad per Cycle by Patient Weight in Each Treatment Course Weight Range [Dose in mg (Number of 10 mg Tablets) per Cycle]

Kg	First Cycle	Second Cycle
40* to less than 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to less than 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to less than 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to less than 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to less than 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to less than 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to less than 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

*The use in patients weighing less than 40 kg has not been investigated. Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days. Do not administer more than 2 tablets daily.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-Approved:

Cladribine (Mavenclad) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. It 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 due to the safety profile.

- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Assessments of the following are required prior to starting each treatment course: cancer screening, pregnancy in females of reproductive potential, complete blood count with differential including lymphocytes, HIV infection, screening for tuberculosis, hepatitis B and C, active infection, varicella zoster antibody testing, immunizations, baseline MRI due to risk of progressive multifocal leukoencephalopathy (PML), and liver enzymes.
- The cumulative dosage of 3.5 mg/kg is administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course given 43 weeks apart). Each course is divided into 2 treatment cycles (separated by 23 to 27 days). Separate from other oral drugs by at least 3 hours during the treatment cycles. See prescribing information for dosing information. Following the administration of 2 treatment courses, do not administer additional treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. Treatment more than 2 years after completing 2 treatment courses has not been studied.

Dimethyl fumarate (Tecfidera)

Dimethyl fumarate (Tecfidera) is indicated for the treatment of persons with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. The recommended initial dose is 120 mg twice daily for 7 days, followed by 240 mg twice daily thereafter. Temporary dose reduction to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dosage of 240 mg twice a day should be resumed. Discontinuation should be considered for patients unable to tolerate return to the maintenance dosage. Administration with food or with a non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dosing may reduce the incidence or severity of flushing. Dimethyl fumarate can be administered without regard to meals and the capsules should be swallowed whole and intact. Members should be instructed not to crush, chew, or sprinkle the capsule contents on food. Inform patients they will be provided with two strengths when starting treatment.

Diroximel fumarate (Vumerity)

Diroximel fumarate (Vumerity) is indicated for the treatment of persons with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. The recommended initial dose is 231 mg twice daily for 7 days, followed

by 462 mg twice daily thereafter. Temporary dose reduction to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dosage of 462 mg twice a day should be resumed. Discontinuation should be considered for patients unable to tolerate return to the maintenance dosage. Administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dosing may reduce the incidence or severity of flushing. Diroximel fumarate should not be administered with a high-fat, high-calorie meal. If taken with food, the meal should contain no more than 700 calories and no more than 30 g of fat. Avoid co-administration with alcohol. The capsules should be swallowed whole and intact. Members should be instructed not to crush, chew, or sprinkle the capsule contents on food.

Fingolimod capsule (Gilenya) is administered as 0.5 mg oral capsule once daily in adults and pediatric patients 10 years of age and older weighing more than 40 kg, with or without food. For patients less than or equal to 40 kg and 10 years of age and older, administer 0.25 mg oral capsule once-daily, with or without food. Fingolimod orally disentigrating tablet (Tascenso ODT) is approved for the treatment of relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older. For patients who weigh less than or equal to 40 kg, the dose is a 0.25 mg daily. For patients greater than 40 kg, the dose is 0.5 mg daily. The tablet should be taken with or without food. The tablet should be administered immediately after removal from the blister pack and is placed directly on the tongue, then allowed to dissolve before swallowing. See prescribing information for baseline assessments and first dose monitoring prior to initiating therapy.

Interferon products and Glatiramer acetate

Drug	FDA-approved indication	Usual Dosage	Comments
Avonex (IFN beta-1a)	Relapsing forms of MS†	30 mcg IM once a week	If a dose is missed, it should be given as soon as possible; do not give 2 injections within 2 days of each other
Rebif (IFN beta-1a)	Relapsing forms of MS†	22 or 44 mcg SQ three times weekly	Each dose should be given at least 48 hours apart. Refer to the package insert for titration schedule.
Plegridy (pegIFN beta-1a)	Relapsing forms of MS†	125 mcg every 14 days	For SQ injection only
Betaseron (IFN beta-1b)	Relapsing forms of MS†	0.25 mg SQ every other day	Refer to the package insert for titration schedule.
Extavia (IFN beta-1b)	Relapsing forms of MS†	0.25 mg SQ every other day	
Copaxone (glatiramer acetate)	Relapsing forms of MS†	20 mg SQ daily or 40 mg SQ three times a week	For SQ injection only; allow solution to warm to room temperature.
†Includes clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. IFN=Interferon; IM=Intramuscularly; SQ=Subcutaneously			

Monomethyl fumarate (**Bafiertam)**

Monomethyl fumarate (Bafiertam) 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. The initial dose is 95 mg twice a day orally for 7 days, followed by 190 mg (administered as two 95 mg capsules) twice a day orally thereafter. Temporary dosage reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dosage. Within 4 weeks, the recommended dosage of 190 mg twice a day should be resumed. Discontinuation should be considered for patients unable to tolerate return to the maintenance dosage. Administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dosing may reduce the incidence or severity of flushing. Monomethyl fumarate can be taken with or without food. The capsules should be swallowed whole and intact. Members should not crush, chew, or mix the contents with food.

Ofatumumab (Kesimpta) For relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults:

- initial dosing: 20 mg by subcutaneous injection at Weeks 0, 1, and 2
- subsequent dosing: 20 mg by subcutaneous injection once monthly starting at Week 4

Administer in the abdomen, thigh, or outer upper arm subcutaneously. Do not give injection into moles, scars, stretch marks or areas where the skin is tender, bruised, red, scaly, or hard.

Ponesimod (Ponvory)

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.

Treatment Initiation

A starter pack must be used for patients initiating treatment. Initiate treatment with a 14-day titration; start with one 2 mg tablet orally once daily and progress with the titration schedule as below:

Titration Day Daily Dose	Mg
Days 1 and 2	2 mg
Days 3 and 4	3 mg
Days 5 and 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Days 12, 13, and 14	10 mg

Maintenance Daily Dose

Day 15 and thereafter: 20 mg

See prescribing information for initial assessments and dose adjustment.

Siponimod (Mayzent) is approved 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. Test patients for CYP2C9 variants to determine genotype prior to treatment. Assess all of the following prior to treatment: complete blood count, an ophthalmic evaluation, cardiac evaluation, liver function test, skin examination, varicella zoster antibody testing and current or prior use of immunosuppressive medications,. First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure.

- CYP2C9*1/*1 or *1/*2, or *2/*2 genotype: Titration is required for the first 5 days of treatment initiation. See prescribing information for the titration regimen. The recommended maintenance dosage is 2 mg.
- CYP2C9*1/*3 or *2/*3 genotype: Titration is required for the first 4 days of treatment initiation. See prescribing information for the titration regimen. The recommended maintenance dose in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg.

Teriflunomide (Aubagio) is approved for the treatment of members with relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended dose is 7- or 14 mg orally once daily, with or without food. See prescribing information for dose adjustment prior to initiating therapy.

Drug Availability:

Aubagio (Teriflunomide)	• 7- and 14 mg film-coated tablets
Avonex (IFN beta-1a)	• 30 mcg/0.5 mL prefilled syringe • 30 mcg/0.5 mL auto-injector for injection
Bafiertam (Monomethyl fumarate)	• 95 mg delayed-release capsules
Betaseron (IFN beta-1b)	• 0.3 mg powder for injection kit (contains a single-use vial and a prefilled single-use syringe containing 1.2 mL of diluent)
Cladribine (Mavenclad)	• 10 mg tablets
Copaxone (glatiramer acetate)	• 20 mg/mL or 40 mg/mL prefilled syringe
Extavia (IFN beta-1b)	• 0.3 mg powder for injection kit (contains a single-use vial and a prefilled single-use syringe containing 1.2 mL of diluent)
Gilenya (Fingolimod)	• 0.25 mg and 0.5 mg capsule. Fingolimod (Tascenso ODT) is supplied as a 0.25 mg and 0.5 mg tablet.
Kesimpta (Ofatumumab)	• 20 mg/0.4 mL in a single-dose prefilled Sensoready Pen and single-dose prefilled syringe
Mayzent (Siponimod)	• 0.25 mg and 2 mg tablets

Plegridy (PegIFN beta-1a)	• 125 mcg/0.5 mL prefilled pen • 125 mcg/0.5 mL prefilled syringe • Starter pack: 63 mcg/0.5 mL prefilled pen, 0.94 mcg/0.5 mL prefilled pen, 125 mcg/0.5 mL prefilled pen • Starter pack: 63 mcg/0.5 mL prefilled syringe, 0.94 mcg/0.5 mL prefilled syringe, 125 mcg/0.5 mL prefilled syringe
Ponvory (Ponesimod)	• 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg Tablets
Rebif (IFN beta-1a)	• 22 mcg/0.5 mL prefilled syringe or auto-injector • 44 mcg/0.5 mL prefilled syringe or auto-injector Titration pack (contains six 22 mcg/0.5 mL and six 8.8 mcg/0.2 mL prefilled syringes or auto-injector
Tecfidera (Dimethyl fumerate)	• 120- and 240 mg delayed-release capsules
Vumerity (Diroximel fumarate)	• 231 mg delayed-release capsules.
IFN=Interferon	

PRECAUTIONS:

Cladribine (Mavenclad)

Boxed Warning

- Malignancies: cladribine may increase the risk of malignancy and is contraindicated in patients with current malignancy; evaluate benefits and risks on an individual basis for patients with prior or increased risk of malignancy.
- Teratogenicity: cladribine is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm

Contraindications

- Current malignancy
- Pregnant women
- Women and men of reproductive potential who do not plan to use effective contraception during treatment or for at least 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 treatment day and for 10 days after the last dose

Precautions/Warnings

- Malignancy risk is increased and benefits and risks of use in patients with prior malignancy or increased risk should be evaluated.
- Risk of teratogenicity can occur and pregnancy should be excluded prior to treatment. Effective contraception should be used during treatment and up to 6 months after the last dose in each treatment course in women and men of reproductive potential.
- Lymphopenia: Monitor lymphocyte counts before, during and after treatment.
- Infections: Serious, life-threatening infections have been reported. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections.
- Progressive multifocal leukoencephalopathy (PML) has been reported in postmarketing studies of parenteral cladribine for oncology indications. A baseline MRI should be obtained before initiating the first treatment course of cladribine.
- Administer all immunizations according to guidelines prior to cladribine. Live vaccines should be administered at least 4 to 6 weeks prior to starting cladribine due to risk of active vaccine infection. Avoid live vaccines during and after cladribine while white blood cell counts are not within normal limits.
- Hematologic toxicity: Monitor complete blood count before, during and after treatment.
- Graft-versus-host-disease with blood transfusion: Irradiation of cellular blood components is recommended to decrease the risk of transfusion-associated graft-versus-host disease.
- Liver injury: Clinically significant and life-threatening liver injury has been reported. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to each treatment cycle and course. Discontinue if clinically significant injury is suspected. Use is not recommended with moderate to severe hepatic impairment.
- Hypersensitivity reactions have occurred. Do not use in patients with a history of hypersensitivity.
- Cardiac failure has occurred with both oral and parenteral cladribine.

Dimethyl fumarate(Tecfidera), Diroximel fumarate (Vumerity), Monomethyl fumarate (Bafiertam)
Contraindications

- Known hypersensitivity to dimethyl fumarate, diroximel fumarate, monomethyl fumarate or any of the excipients.
- Co-administration with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate,

Dimethyl fumarate(Tecfidera), Diroximel fumarate (Vumerity), Monomethyl fumarate (Bafiertam)

Precautions/Warnings

- **Anaphylaxis and angioedema**: discontinue and do not restart therapy if this occurs.
- **Herpes zoster and other serious opportunistic infections:** withhold for serious infection until resolution.
- **Progressive multifocal leukoencephalopathy (PML)**: withhold at the first sign or symptom suggestive of PML.

- **Liver injury**: Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating and during treatment, as clinically indicated. Discontinue if clinically significant liver injury is suspected.
- **Lymphopenia:** may decrease lymphocyte counts; prior to therapy initiation, a recent complete blood count should be available. Monitor CBC after 6 months and every 6 to 12 months thereafter. Interrupt treatment if lymphocyte counts less than 0.5 x 10^9/L persist for more than 6 months.
- **Flushing:** in clinical trials, 40% of dimethyl fumarate treated subjects experienced flushing. Symptoms typically began soon after therapy initiation and usually improved over time. Administration with non-enteric coated aspirin (up to 325 mg) 30 minutes prior may reduce the incidence of flushing. Dimethyl fumarate may also be administered with food to improve flushing symptoms.
- **Serious Gastrointestinal reactions**: Serious gastrointestinal reactions, including perforation, ulceration, hemorrhage, and obstruction, some fatal outcomes, have been reported in the postmarketing setting with the use of fumaric acid esters, including dimethyl fumarate, with or without concomitant aspirin use.
- **Pregnancy and Lactation**: No adequate and well-controlled studies in pregnant women have been conducted, see prescribing information.

Fingolimod (Gilenya) Contraindications

- Members with a history (within the last 6 months) of myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure with hospitalization or Class III/IV heart failure
- Members with a history or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome, unless member has a functioning pacemaker
- Members with a baseline QTc interval of ≥ 500 ms
- Members prescribed concomitant Class Ia or Class III anti-arrhythmic therapy
- Members with hypersensitivity to fingolimod or its excipients

Fingolimod (Gilenya) Warnings/Precautions

- **Infection:** fingolimod therapy my increase the risk of infection. A recent complete blood count (CBC) should be available prior to fingolimod initiation. Members should be monitored for signs and symptoms of infection during treatment and for two months after discontinuation. Fingolimod should not be initiated in members with active acute or chronic infections. All members receiving fingolimod should receive the varicella vaccine, or have evidence of antibodies to varicella zoster virus.
- **Progressive multifocal leukoencephalopathy (PML**): withhold at the first sign or symptom suggestive of PML. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with fingolimod who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. Monitor for development of IRIS.

- **Macular edema:** macular edema can occur with or without visual symptoms. An ophthalmologic evaluation should be performed before and re-evaluated at 3-4 months following fingolimod initiation. Visual acuity should be monitored at baseline and during routine evaluation of members. Members with diabetes mellitus or a history of uveitis are at an increased risk for macular edema and should have regular ophthalmologic evaluation
- **Malignancies:** suspicious skin lesions should be evaluated. An increase in the incidence of cutaneous malignancies including basal cell carcinoma (BCC) and melanoma occurred in clinical trials as compared to placebo. Cases of lymphoma have also occurred including T-cell, B-cell, and CNS lymphoma.
- **Posterior reversible encephalopathy syndrome (PRES):** Rare cases of PRES have occurred. Symptoms may include sudden onset of severe headache, altered mental status, visual disturbances, and seizure. If suspected discontinue.
- **Respiratory effects:** fingolimod therapy has been associated with a decrease in pulmonary function tests. Spirometry and diffusion lung capacity for carbon monoxide should be obtained when clinically indicated.
- **Hepatic effects:** fingolimod therapy has been associated with increases in liver transaminases. Liver function tests (LFTs) should be obtained prior to fingolimod initiation and assessed if hepatic injury is suspected. If significant liver injury occurs, fingolimod should be discontinued.
- **Pregnancy and Nursing:**
    - Female members of childbearing potential should be advised to use effective contraception during treatment and 2 months after stopping fingolimod. Fingolimod is excreted into the milk of lactating rats and excretion into human milk is probable.
- **Severe Increase in Disability after stopping**: monitor for development of severe increase in disability following discontinuation and begin appropriate treatment as needed.
- **Tumefactive MS:** consider when severe MS relapse occurs during treatment of after discontinuation.
- **Increased blood pressure**: monitor during treatment. Increases in blood pressure occurred in clinical trials as compared to placebo.
- **Immune system effects following discontinuation**: Fingolimod remains in the blood for up to 2 months following the last dose. Lymphocyte counts may be affected during this time and precaution is advised with initiation of other drugs during this time.
- **Hypersensitivity reactions**: Reactions including rash, urticaria, and angioedema have been reported.

Glatiramer acetate

Contraindications: persons with a history of hypersensitivity to glatiramer acetate or mannitol

Glatiramer acetate products (Copaxone)

Precautions/warnings

- **Life-threatening and fatal anaphylaxis**: Anaphylaxis can occur at any time following initiation from the first dose up to years after initial treatment. Most cases occurred within an hour after the injection. Signs may overlap with immediate post-injection reactions.
- **Immediate post-injection reaction:** a constellation of symptoms immediately after injection that includes at least 2 of the following: anxiety, chest pain, constriction of the throat, dyspnea, flushing, palpitations, and urticaria. In general, it is typically transient and self-limiting and occurs after the first few months of treatment. This reaction may occur more than once in a given member.
- **Chest pain**: Transient chest pain - without any long-term effects - may occur one or more times, either as part of the post-injection reaction or separately. While some of these episodes occurred in the context of the immediate post-injection reaction previously described, many did not.
- **Lipoatrophy and skin necrosis:** Localized lipoatrophy and, rarely, injection site skin necrosis at injection sites have been reported during post-marketing experience. Careful rotation of injection sites is recommended so no single area is used for injections more than one time per week.
- **Effect on Immune response:** Because glatiramer can modify immune response, it may interfere with immune functions. For example, treatment with glatiramer may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. Glatiramer acetate-reactive antibodies are formed in most patients receiving glatiramer acetate.
- **Hepatic Injury**: cases of hepatic injury, some severe, including liver failure and hepatitis have been reported. This has occurred from days to years after initiating treatment. If signs or symptoms occur, consider discontinuation.
- **Injection errors**: using an optional autoinjector that is not compatible may increase the risk for medication errors, such as dose omission or administration of a partial dose.
- **Children:** The safety and efficacy of glatiramer have not been established in patients younger than 18 years of age.
- **Pregnancy and Nursing:**
    - There are no adequate and well-controlled studies of glatiramer acetate in pregnant women; however, administration of glatiramer acetate to pregnant rats and rabbits resulted in no adverse effects on fetal development at doses up to 37.5 mg/kg/day (18 and 36 time, respectively, the therapeutic human dose of 20 mg/day on a mg/m2 basis).
    - No human studies have investigated the effects of glatiramer acetate on breast-fed infants and caution in nursing women is recommended.

Interferon beta (Avonex, Rebif, Betaseron, Extavia, Plegridy):

Contraindications: persons with a history of hypersensitivity to interferon beta or albumin (human)

Precautions/warnings

- **Hepatic injury:** monitor liver function tests. Consider discontinuation if hepatic injury occurs.

- **Depression, suicide, and psychotic disorders:** Monitor and report any symptoms. Consider discontinuation if depression occurs. Use with caution in persons with depression.
- **Injection site necrosis:** Typically, injection site necrosis occurs within the first 4 months of therapy; however, post-marketing reports of injection site necrosis occurring over 1 year after initiation of therapy have been received. Necrosis may occur at single or multiple injection sites. Injection sites should be rotated on a regular basis and do not administer into the affected area until fully healed.
- **Anaphylaxis:** Rare but significant allergic reactions can occur following interferon beta therapy.
- **Autoimmune disorders:** There have been post-marketing reports of autoimmune disorders of multiple target organs, including idiopathic thrombocytopenia and hyper- and hypothyroidism. Rare cases of autoimmune hepatitis have also been reported. Monitor patients for signs of these disorders and consider discontinuation.
- **Seizures:** Use with caution in patients with preexisting seizure disorders. A relationship between occurrence of seizures and the use of Avonex® has not been established.
- **Decreased peripheral blood counts:** monitor complete blood counts.
- **Thrombotic microangiopathy (TMA):** cases have been reported. Discontinue if TMA occurs.
- **Pulmonary Arterial Hypertension**: cases of pulmonary arterial hypertension (PAH) have been reported in patients treated with interferon beta products.
- **Congestive heart failure:** monitor with preexisting cardiac disease or worsening cardiac symptoms.
- **Children:** The safety and efficacy of glatiramer have not been established in persons younger than 18 years of age.
- **Pregnancy and Nursing:**
    - There are no adequate and well-controlled studies of interferon beta preparations in pregnant women.
    - Additionally, no human studies have investigated the effects of interferon beta in breast-fed infants. According to the manufacturers of Betaseron and Extavia, these agents should be avoided in breast feeding. The manufacturers of Avonex and Rebif recommend cautious use of either product in nursing women.

Ofatumumab (Kesimpta)

Boxed Warning

- none

Contraindications

- Active Hepatitis B Virus (HBV) infection
- History of hypersensitivity or life-threatening injection-related reaction to ofatumumab

Precautions/Warnings

- **Infections:** Serious, including life-threatening and fatal infections have occurred. Delay administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion.
- **Injection-Related Reactions:** Management for injection-related reactions and hypersensitivity reactions depends on the type and severity of the reaction.
- **Reduction in Immunoglobulins:** Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment until B-cell repletion. Consider discontinuing if a patient develops a serious
- opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise.
- **Fetal Risk:** May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping.

Ponesimod (Ponvory)

Contraindications

- 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

Precautions/Warnings

- Infections: may increase the risk of infections. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Do not start treatment in patients with active infection.
- Bradyarrhythmia and Atrioventricular Conduction Delays: use may result in a transient decrease in heart rate; titration is required for treatment initiation.Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting treatment. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate.
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating treatment.
- Increased Blood Pressure (BP): Monitor BP during treatment.
- Cutaneous Malignancies: Skin examination prior to treatment and periodically is recommended.
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 1 week after stopping treatment.

- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking ponesimod. Diabetes mellitus and uveitis increase the risk.
- Progressive multifocal leukoencephalopathy (PML): withhold at the first sign or symptom suggestive of PML. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with fingolimod who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. Monitor for development of IRIS.
- Severe Increase in disability after stopping: severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation. After stopping in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS).
- Immune system effects: the half-life and mode of action should be considered when switching from drugs with prolonged immune effects to avoid additive effects on the immune system. Ponesimod remains in the blood for up to 1 week, and pharmacodynamic effects may persist for 1 to 2 weeks after the last dose.

Siponimod (Mayzent)

Boxed Warning

- none

Contraindications

- CYP2C9*3/*3 genotype.
- In the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III or IV heart failure.
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker.

Precautions/Warnings

- **Infection risk**: Obtain a complete blood count and monitor for infection. Do not start treatment in patients with an active infection. A dose-dependent reduction in peripheral lymphocyte count to 20-30% of baseline values occurs because of reversible sequestration of lymphocytes in lymphoid tissues.
- **Macular edema**: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision. Diabetes mellitus and uveitis increase the risk.
- **Bradyarrhythmia and Atrioventricular conduction delays:** Titration is required for treatment initiation. Consider cardiologist consultation before use with other drugs that decrease heart rate. Consider resting heart rate prior to concomitant beta-blocker use.
- **Respiratory Effects:** Pulmonary function should be assessed and may decline with treatment
- **Liver Injury:** Liver function should be assessed prior to treatment and monitored closely in patients with severe hepatic impairment.
- **Cutaneous Malignancies:** Skin examination at the start of treatment and periodically is recommended.

- **Increased Blood pressure:** Blood pressure should be monitored and could increase during treatment.
- **Fetal risk:** Women should use contraception during and for 10 days after stopping treatment due to potential fetal risk.
- **Progressive multifocal leukoencephalopathy (PML):** withhold at the first sign or symptom suggestive of PML. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with fingolimod who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. Monitor for development of IRIS.
- Posterior reversible encephalopathy syndrome has been reported in patients receiving a sphingosine 1-phosphate receptor modulator.
- There is an unintended additive immunosuppressive effects from prior treatment with immunosuppressive modulating therapies; do not initiate treatment following alemtuzumab.
- Severe increase in disability after discontinuation is possible.
- Immune system effects after discontinuation may persist for up to 4 weeks after treatment is stopped.
- Live vaccines should be avoided during treatment and for up to 4 weeks after treatment is stopped.
- Use is not recommended with moderate CYP2C9 and moderate or strong CYP3A4 inhibitors; use may result in increased exposure to siponimod.
- Use is not recommended with moderate CYP2C9 and strong CYP3A4 inducers; use may result in decreased exposure to siponimod.

Teriflunomide (Aubagio)

Boxed Warnings

- **Hepatotoxicity:** Severe liver injury including fatal liver failure has been reported in individuals administered leflunomide. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.
    - Obtain transaminase and bilirubin levels within 6 months before initiation of teriflunomide and monitor transaminase levels at least monthly for 6 months.
    - If drug induced liver injury is suspected, discontinue teriflunomide and perform accelerated elimination procedure.
- **Risk of Teratogenicity:** Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment. Use effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure.

Teriflunomide (Aubagio) Contraindications

- Severe Hepatic Impairment
- Pregnant women or women of childbearing potential not using reliable contraception may cause fetal harm.
- Hypersensitivity to teriflunomide, leflunomide or any of the inactive ingredients.

- Concomitant leflunomide

Teriflunomide (Aubagio) Warnings/Precautions

Peripheral Neuropathy: If a member develops symptoms consistent with peripheral neuropathy, evaluate member and consider discontinuing teriflunomide and using accelerated elimination procedure. Members greater than 60 years of age, with concomitant nephrotoxic medications, and diabetes may be at an increased risk of peripheral neuropathy.

Hypersensitivity, Severe skin reaction, and Drug Reaction with Eosinophilia and Systemic Symptoms: cases of anaphylaxis, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Fatal outcomes have been reported. If members administered teriflunomide develop signs and symptoms of severe allergic reaction, SJS, TEN, or DRESS, discontinue teriflunomide, seek medical care, and perform an accelerated elimination procedure.

Blood pressure: teriflunomide may affect blood pressure. Blood pressure should be measured at treatment initiation and periodically during treatment. Elevated blood pressure should be appropriately managed during treatment.

Concomitant use with immunosuppressive or immunomodulating therapies: Co-administration with antineoplastic, or immunosuppressive therapies used for the treatment of MS has not been evaluated. Although safety studies in which teriflunomide was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns, the long-term safety of these combinations has not been established.

Bone marrow effects: A decrease in white blood cell (WBC) count may occur in members treated with teriflunomide. In clinical trials, the decrease in WBC count occurred during the first 6 weeks and the count remained low during treatment. Although no cases of serious pancytopenia were reported in premarketing trials of teriflunomide, rare cases of pancytopenia, agranulocytosis, and thrombocytopenia have been reported in the postmarketing setting with leflunomide. Obtain a complete blood count (CBC) within 6 months before the initiation of teriflunomide treatment. Additional monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

Risk of Infection: teriflunomide should not be initiated in members with active acute or chronic infections until the infection is resolved. If a member develops serious infection while taking teriflunomide, consider suspending treatment and using an accelerated elimination procedure.

Respiratory effects: Interstitial lung disease, including acute interstitial pneumonitis has been reported.

Tuberculosis screening: members should be screened for latent tuberculosis infection with a tuberculin skin test prior to initiating teriflunomide. The safety of teriflunomide in individuals with a positive tuberculin skin test is unknown.

Pancreatitis in Pediatric Patients: cases of pancreatitis were observed in 1.8% (2/109) of pediatric patients receiving teriflunomide.

Pregnancy and Lactation

- Teriflunomide is contraindicated in pregnancy and women of childbearing potential who are not using reliable contraception. Teratogenicity and embryofetal lethality occurred in animal reproduction studies in multiple animal species. Exclude pregnancy prior to treatment in women of childbearing potential. If a woman becomes pregnant, treatment should be discontinued, and an accelerated drug elimination procedure should occur.
- Additionally, teriflunomide is detected in human semen. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of teriflunomide and undergo an accelerated elimination procedure.
- It is not known if teriflunomide is excreted in human milk; however, it was detected in rat milk following a single oral dose.
- Elimination can be accelerated by administration of cholestyramine or activated charcoal for 11 days.

BILLING/CODING INFORMATION:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Kesimpta, Plegridy)
J1595	Injection, glatiramer acetate, 20 mg (Copaxone)
J1826	Injection, interferon beta-1a, 30 mcg (Avonex)
J1830	Injection, interferon beta-1b, 0.25 mg (Betaseron, Extavia)
J3590	Unclassified biologic (Plegridy)
J8499	Prescription drug, oral, nonchemotherapeutic, NOS
Q3027	Injection, interferon beta-1a, 1 mcg for subcutaneous use (Avonex)
Q3028	Injection, interferon beta-1a, 1 mcg for subcutaneous use (Rebif)

ICD-10 Diagnosis Codes That Support Medical Necessity

G35.A	Relapsing-remitting multiple sclerosis
G35.C1	Active secondary progressive multiple sclerosis
G37.9	Demyelinating disease of central nervous system, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination

(LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of individuals with MS.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of individuals.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS.

RELATED GUIDELINES:

Alemtuzumab (Lemtrada), 09-J2000-27

Natalizumab (Tysabri®) IV, 09-J0000-73

Ocrelizumab (Ocrevus), 09-J2000-78

Ozanimod (Zeposia), 09-J3000-70

Ublituximab-xiiy (Briumvi™), 09-J4000-45

OTHER:

None.

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025-05-28]. Available from: http://www.clinicalpharmacology.com/.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025-05-28].
3. Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. Available at http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed 09/26/2016.
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2025-05-28]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

5. 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. April 2018. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/898

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

03/15/26	Consolidation of multiple sclerosis oral agents and self-injectable therapy into a single medical coverage guideline.