Clinical Policy: Multiple Sclerosis Drugs

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Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are multiple sclerosis drugs requiring prior authorization: alemtuzumab (Lemtrada®), cladribine (Mavenclad®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), monomethyl fumarate (Bafiertam), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), ofatumumab (Kesimpta®), ozanimod (Zeposia®), peginterferon beta-1a (Plegridy®), siponimod (Mayzent®), and teriflunomide (Aubagio®).

FDA Approved Indication(s)

	Clinically Isolated Syndrome (CIS)	Relapsing-Remitting Multiple Sclerosis (RRMS)	Secondary Progressive Multiple Sclerosis (SPMS)	Primary Progressive Multiple Sclerosis (PPMS)
Lemtrada		X	X	
Mavenclad		X	X	
Tecfidera	X	X	X	
Vumerity	X	X	X	
Gilenya	X	X	X	
Copaxone/Glatopa	X	X	X	
Avonex/Rebif	X	X	X	
Betaseron/Extavia	X	X	X	
Novantrone		X	X	
Bafiertam	X	X	X	
Tysabri	X	X	X	
Ocrevus	X	X	X	X
Kesimpta	X	X	X	
Zeposia	X	X	X	
Plegridy	X	X	X	
Mayzent	X	X	X	
Aubagio	X	X	X	

AHCCCS preferred drugs in this class include Gilenya® (fingolimod), Copaxone® 20 mg, Glatopa® 40 mg (glatiramer acetate), Avonex®, Rebif Rebidose® (interferon beta-1a), Betaseron® (interferon beta-1b).

AHCCCS non-preferred drugs in this class include alemtuzumab (Lemtrada®), cladribine (Mavenclad®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), Copaxone® 40 mg, Glatopa® 20 mg (glatiramer acetate), interferon beta-1b (Extavia®), mitoxantrone

(Novantrone®), monomethyl fumarate (Bafiertam), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), ofatumumab (Kesimpta®), ozanimod (Zeposia®), peginterferon beta-1a (Plegridy®), siponimod (Mayzent®), and teriflunomide (Aubagio®).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Arizona Complete Health-Complete Care Plan and Care1st that Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Lemtrada, Mavenclad, Mayzent, Novantrone, Ocrevus, Plegridy, Rebif, Tecfidera, Tysabri, Vumerity, and Zeposia are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Avonex, Betaseron, Copaxone 20 mg, Gilenya, Glatopa 40 mg, Rebif (must meet all):

1. Diagnosis of multiple sclerosis (MS): clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), or secondary progressive multiple sclerosis (SPMS);
2. Prescribed by or in consultation with a neurologist;
3. Member's age is one of the following:
   a. For Rebif: age ≥ 2 years;
   b. For Betaseron: age ≥ 12 years;
   c. For Gilenya: age ≥ 10 years;
   d. For Avonex, Copaxone 20 mg, Glatopa 40 mg: age ≥ 18 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. For Gilenya requests, member does not have baseline QTc interval > 500 msec;
7. Dose does not exceed maximum dose indicated in Section V.

Approval duration: 6 months

B. Extavia (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome (CIS), and member is contraindicated to both or has experienced clinically significant adverse effects to one of the following at up to maximally indicated doses: an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   b. Relapsing-remitting multiple sclerosis (RRMS), and failure of Betaseron and one of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Gilenya™, an interferon-beta agent (Avonex®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   c. Secondary progressive multiple sclerosis (SPMS);

2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 12 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. Dose does not exceed maximum dose indicated in Section V.

Approval duration: 6 months

C. Aubagio, **Bafiertam**, **Kesimpta**, **Mayzent**, **Plegridy**, **Tecfidera**, **Vumerity**, **Zeposia** (must meet all):

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome (CIS), and member is contraindicated to both or has experienced clinically significant adverse effects to one of the following at up to maximally indicated doses: an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   b. Relapsing-remitting multiple sclerosis (RRMS), and failure of TWO of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Gilenya™, an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   c. Secondary progressive multiple sclerosis (SPMS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. For Aubagio request, member is not receiving leflunomide;
7. For Kesimpta request, member does not have active hepatitis B infection (positive results for hepatitis B surface antigen and anti-hepatitis B virus tests);
8. For Mayzent requests, documentation that member does not have a CYP2C9*3/*3 genotype (*see Appendix D);*
9. For brand Tecfidera requests, medical justification supports inability to use generic dimethyl fumarate (e.g., contraindications to the excipients of generic product);
10. Dose does not exceed maximum dose indicated in Section V.

Approval duration: 6 months

D. Lemtrada (must meet all):

1. Diagnosis of one of the following (a or b):
   a. Relapsing-remitting multiple sclerosis (RRMS);
   b. Secondary progressive multiple sclerosis (SPMS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;

4. Failure of Gilenya AND one of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
5. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
6. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
7. Dose does not exceed:
   a. First treatment course: 12 mg per day for 5 consecutive days (60 mg total);
   b. Second or subsequent treatment courses: 12 mg per day for 3 consecutive days (36 mg total).

Approval duration: 6 months

E. Mavenclad, **Novantrone** (must meet all):
1. Diagnosis of one of the following (a or b):
   a. Relapsing-remitting multiple sclerosis (RRMS), and failure of TWO of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Gilenya™, an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   b. Secondary progressive multiple sclerosis (SPMS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. Dose does not exceed maximum dose indicated in Section V.

Approval duration: 6 months

F. Ocrevus (must met all):
1. Diagnosis of one of the following (a, b, c, or d):
   a. Clinically isolated syndrome, and member is contraindicated to both or has experienced clinically significant adverse effects to one of the following at up to maximally indicated doses: an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   b. Relapsing-remitting multiple sclerosis (RRMS), and failure of TWO of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Gilenya™, an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   c. Secondary progressive multiple sclerosis (SPMS);
   d. Primary progressive multiple sclerosis (PPMS);
2. Prescribed by or in consultation with a neurologist;

3. Age ≥ 18 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. At the time of request, member does not have active hepatitis B infection (positive results for hepatitis B surface antigen and anti-hepatitis B virus tests);
7. Dose does not exceed the following:
   a. Initial dose: 300 mg, followed by a second 300 mg dose 2 weeks later;
   b. Maintenance dose: 600 mg every 6 months.

Approval duration: 6 months

G. Tysabri (must meet all):

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome, and member is contraindicated to both or has experienced clinically significant adverse effects to one of the following at up to maximally indicated doses: an interferon-beta agent (Avonex®, Betaseron®, Rebif®), glatiramer (Copaxone®, Glatopa®);
   b. Relapsing-remitting multiple sclerosis (RRMS), and failure of Gilenya™ at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   c. Secondary progressive multiple sclerosis (SPMS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Member is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
6. Dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 6 months

H. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid; or
2. Novantrone for diagnoses other than multiple sclerosis: Refer to the Novantrone policy CP.PHAR.258; or
3. Tysabri for Crohn's Disease: Refer to the AZ.CP.PHAR.06 Cytokine and CAM Antagonists policy; or
4. Ofatumumab (Arzerra) for diagnoses other than multiple sclerosis: Refer to CP.PHAR.306.

II. Continued Therapy

A. All Drugs in Section I for Multiple Sclerosis (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. If member has received < 1 year of total treatment: Member is responding positively to therapy;
   b. If member has received ≥ 1 year of total treatment: Member meets one of the following (i, ii, iii, or iv):
      i. Member has not had an increase in the number of relapses per year compared to baseline;
      ii. Member has not had ≥ 2 new MRI-detected lesions;
      iii. Member has not had an increase in EDSS score from baseline (*see Appendix D*);
      iv. Medical justification supports that member is responding positively to therapy;
3. Drug is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
4. For Lemtrada requests**:** It has been at least 12 months since completion of the prior treatment course;
5. If request is for a dose increase, new dose does not maximum dose indicated in Section V.

Approval duration: first-reauthorization: 6 months; **second and subsequent reauthorizations:** 12 months (*Lemtrada: 1 treatment course only, Mavenclad: up to 1 course, 2 courses lifetime total*)

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid; or
3. Novantrone for diagnoses other than RRMS and SPMS: Refer to the Novantrone policy CP.PHAR.258; or
4. Tysabri for Crohn's Disease: Refer to the AZ.CP.PHAR.06 Cytokine and CAM Antagonists policy; or
5. Ofatumumab (Arzerra) for diagnoses other than multiple sclerosis: Refer to CP.PHAR.306.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – AZ.CP.PMN.53 for Arizona Medicaid or evidence of coverage documents;

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CIS: clinically isolated syndrome
MS: multiple sclerosis
RRMS: relapsing-remitting MS
EDSS: expanded disability status scale
FDA: Food and Drug Administration
PPMS: primary progressive MS
SPMS: secondary progressive MS

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Avonex®, Rebif® (interferon beta-1a)	*Avonex*: 30 mcg IM Q week *Rebif*: 22 mcg or 44 mcg SC TIW	*Avonex*: 30 mcg/week *Rebif*: 44 mcg TIW
Betaseron® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
glatiramer acetate (Copaxone®, Glatopa®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
Gilenya™ (fingolimod)	0.5 mg PO QD	0.5 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

Drug	Contraindications	Boxed Warnings
Fingolimod (Gilenya)	• Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, 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	None

Drug	Contraindications	Boxed Warnings
Dimethyl Fumarate (Tecfidera)	• Known hypersensitivity to dimethyl fumarate, diroximel fumarate, or any of the excipients of Tecfidera, Vumerity, or Bafiertam; coadministration of Tecfidera, Vumerity, and Bafiertam	None
Interferon beta-1a (Avonex, Rebif)	• History of hypersensitivity to natural or recombinant interferon beta, albumin* or any other component of the formulation **The formerly available lyophilized vial formulation of Avonex is contraindicated in patients with a history of hypersensitivity to albumin (human). This contraindication does not apply to the other Avonex formulations*	None
Interferon beta-1b (Betaseron, Extavia)	• History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol	None
Glatiramer Acetate (Copaxone, Glatopa)	• Known hypersensitivity to glatiramer acetate or mannitol	None
Peginterferon beta-1a (Plegridy)	• History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation	None
Teriflunomide (Aubagio)	• Severe hepatic impairment; pregnancy or females of reproductive potential not using effective contraception; hypersensitivity to teriflunomide, leflunomide or any inactive ingredients in Aubagio; current leflunomide treatment	Hepatoxocity, embryofetal toxicity
Cladribine (Mavenclad)	• 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	Malignancies, risk of teratogenicity

Drug	Contraindications	Boxed Warnings
	• Women intending to breastfeed on a Mavenclad treatment day and for 10 days after the last dose	
Siponimod (Mayzent)	• Patients with a CYP2C9*3/*3 genotype • In the last 6 months, experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure • Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker	None
Alemtuzumab (Lemtrada)	• Hypersensitivity or anaphylactic reactions to alemtuzumab or any of the excipients in Lemtrada, infection with human immunodeficiency virus, active infection	Autoimmunity, infusion reactions, stroke, and malignancies
Mitoxantrone (Novantrone)	• Prior hypersensitivity to mitoxantrone	Cardiotoxicity, secondary leukemia
Ocrelizumab (Ocrevus)	• Active Hepatitis B virus infection • History of life-threatening infusion reaction to Ocrevus	None
Natalizumab (Tysabri)	• Patients who have or have had progressive multifocal leukoencephalopathy • Patients who have had a hypersensitivity reaction to Tysabri	Progressive multifocal leukoencephalopathy
Diroximel Fumarate (Vumerity)	• Known hypersensitivity to dimethyl fumarate, diroximel fumarate, or any of the excipients of Tecfidera, Vumerity, or Bafiertam; coadministration of Tecfidera, Vumerity, and Bafiertam	None
Monomethyl fumarate (Bafiertam)	• Known hypersensitivity to dimethyl fumarate, diroximel fumarate, or any of the excipients of Tecfidera, Vumerity, or Bafiertam; coadministration of Tecfidera, Vumerity, and Bafiertam	None
Ozanimod (Zeposia®)	• In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack,	None

Drug	Contraindications	Boxed Warnings
	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	
Ofatumumab (Kesimpta)	• Active hepatitis B virus infection	None

Appendix D: General Information

- Disease-modifying therapies for MS are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam), fingolimod (Gilenya™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocreliuzmab (Ocrevus™), cladribine (Mavenclad®), siponimod (Mayzent®), and ozanimod (Zeposia®), and ofatumumab (Kesimpta®).
- Of the disease-modifying therapies for MS that are FDA-labeled for CIS, only the interferon products, glatiramer, and Aubagio have demonstrated any efficacy in decreasing the risk of conversion to MS compared to placebo. This is supported by the AAN 2018 MS guidelines.
- Teriflunomide is the principal active metabolite of leflunomide and is responsible for leflunomide's activity in vivo. At recommended doses, teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.
- The CYP2C9 genotype has a significant impact on siponimod metabolism. Mayzent is contraindicated in patients homozygous for CYP2C9*3 (i.e., CYP2C9*3/*3 genotype), which is approximately 0.4%-0.5% of Caucasians and less in others, because of substantially elevated siponimod plasma levels. Mayzent dosage adjustment is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod.
- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya, Tysabri, and Lemtrada for patients with highly active MS. Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.
- Lemtrada is available only through a restricted program under a REMS called the Lemtrada REMS Program because of the risks of autoimmunity, infusion reactions, and malignancies.

- Because of the risk of progressive multifocal leukoencephalopathy, Tysabri is only available through a REMS program called the TOUCH® Prescribing Program.
- Tecfidera and Vumerity are both prodrugs of Bafiertam.

Expanded Disability Status Scale (EDSS)			
Score	**Description**	**Score**	**Description**
0	Normal neurological exam, no disability in any FS	1	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS	2	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS	3	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking	4	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m	5	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m	6	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting

6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transfering. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow

7	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
8	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
9	Confined to bed. Can still communicate and eat
10	Death due to MS

V. Dosage and Administration

Drug	Dosing Regimen	Maximum Dose
Fingolimod (Gilenya)	Adults and pediatric patients 10 years of age and older weighing > 40 kg: 0.5 mg PO QD Pediatric patients 10 years of age and older weighing ≤ 40 kg: 0.25 mg PO QD	0.5 mg/day
Dimethyl Fumarate (Tecfidera)	Starting: 120 mg PO BID X 7 days Maintenance: 240 mg PO BID	480 mg/day

Drug	Dosing Regimen	Maximum Dose
Interferon beta-1a (Avonex, Rebif)	**Avonex:** 30 mcg IM Q week; may be titrated starting with 7.5 mcg for the first week, increased by 7.5 mcg each week for 3 weeks until target of 30 mcg is reached **Rebif:** Initial dose at 20% of prescribed dose TIW increased over 4 weeks to the targeted dose of either 22 mcg or 44 mcg SC TIW	**Avonex:** 30 mcg/wk **Rebif:** 44 mcg TIW
Interferon beta-1b (Betaseron, Extavia)	Generally start at 0.0625 mg SC every other day, and increase over a 6 week period to 0.25 mg SC every other day	0.25 mg QOD
Glatiramer Acetate (Copaxone, Glatopa)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
Peginterferon beta-1a (Plegridy)	63 mcg on day 1, 94 mcg on day 15, and 125 mcg on day 29 and every 14 days thereafter	125 mcg/14 days
Teriflunomide (Aubagio)	7 or 14 mg PO QD with or without food	14 mg/day
Cladribine (Mavenclad)	DOSAGE ADMINISTRATION OVERVIEW • Cumulative dosage of 3.5 mg/kg PO divided into 2 yearly treatment COURSES (1.75 mg/kg per treatment course). • Each treatment COURSE is divided into 2 treatment CYCLES. • See dosage chart in package insert and below for number of tablets per CYCLE based on body weight in kg. • 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. Separate administration from any other oral drug by at least 3 hours. • Following the administration of 2 treatment COURSES, do not administer additional Mavenclad treatment during the next 2 years. Treatment during these 2	2 tablets/day, 10 tablets/cycle 2 cycles/course/year, 2 courses total

Drug	Dosing Regimen	Maximum Dose
	years may further increase the risk of malignancy. The safety and efficacy of reinitiating Mavenclad more than 2 years after completing 2 treatment courses has not been studied. <u>COURSES AND CYCLES</u> • COURSE ONE (year one) Complete pre-treatment assessment. ○ First CYCLE: start any time ○ Second CYCLE: start 23 to 27 days after last dose of first cycle. • COURSE TWO (year two) Complete pre-treatment assessment. ○ First CYCLE: start at least 43 weeks after last dose of first course's second cycle. ○ Second CYCLE: start 23 to 27 days after the last dose of second course's first cycle <u>WEIGHT RANGE (KG): # OF TABLETS – FIRST AND SECOND CYCLES</u> • 40* to less than 50 kg ○ 40 mg (4 tablets) (cycles 1 and 2) • 50 to less than 60 kg ○ 50 mg (5 tablets) (cycles 1 and 2) • 60 to less than 70 kg ○ 60 mg (6 tablets) (cycles 1 and 2) • 70 to less than 80 kg ○ 70 mg (7 tablets) (cycles 1 and 2) • 80 to less than 90 kg ○ 80 mg (8 tablets) (cycle 1) ○ 70 mg (7 tablets) (cycle 2) • 90 to less than 100 kg ○ 90 mg (9 tablets) (cycle 1) ○ 80 mg (8 tablets) (cycle 2) • 100 to less than 110 kg ○ 100 mg (10 tablets) (cycle 1) ○ 90 mg (9 tablets) (cycle 2) • 110 kg and above ○ 100 mg (10 tablets) (cycles 1 and 2)	

Drug	Dosing Regimen	Maximum Dose
	*The use of Mavenclad in patients weighing less than 40 kg has not been investigated.	
Siponimod (Mayzent)	**All patients:** Day 1 and 2: 0.25 mg PO QD Day 3: 0.5 mg PO QD Day 4: 0.75 mg PO QD **CYP2C9 genotypes *1/*1, *1/*2, or *2/*2:** Day 5: 1.25 mg PO QD Day 6 and onward: 2 mg PO QD **CYP2C9 genotypes *1/*3 or *2/*3:** Day 5 and onward: 1 mg PO QD	2 mg/day
Alemtuzumab (Lemtrada)	IV infusion for 2 or more treatment courses: • First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course • Subsequent courses as needed: 12 mg/day on 3 consecutive days 12 months after any prior course	See regimen
Mitoxantrone (Novantrone)	12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months	Cumulative lifetime dose of $\geq$ 140 mg/m^2
Ocrelizumab (Ocrevus)	Initial 300 mg intravenous infusion with a second 300 mg intravenous infusion two weeks later, followed by subsequent doses of 600 mg via intravenous infusion every 6 months	600 mg/6 months
Natalizumab (Tysabri)	300 mg IV every 4 weeks	300 mg/4 weeks
Diroximel Fumarate (Vumerity)	Starting: 231 mg PO BID for 7 days Maintenance: 462 mg PO BID	924 mg/day
Monomethyl fumarate (Bafiertam)	Starting: 95 mg PO BID for 7 days Maintenance: 190 mg PO BID	380 mg/day

Drug	Dosing Regimen	Maximum Dose
Ozanimod (Zeposia®)	Days 1-4: 0.23 mg PO QD Days 5-7: 0.46 mg PO QD Day 8 and thereafter: 0.92 mg PO QD If a dose of Zeposia is missed during the first 2 weeks of treatment, reinitiate treatment using the titration regimen. If a dose of Zeposia is missed after the first 2 weeks of treatment, continue with the treatment as planned.	0.92 mg/day
Ofatumumab (Kesimpta)	20 mg SC at weeks 0, 1, and 2, followed by 20 mg SC monthly starting at week 4	20 mg

VI. Product Availability

Drug	Availability
Fingolimod (Gilenya)	Capsule: 0.25 mg, 0.5 mg
Dimethyl Fumarate (Tecfidera)	Delayed-release capsules: 120 mg, 240 mg
Interferon beta-1a (Avonex, Rebif)	**Avonex:** Single-use prefilled autoinjector or syringe: 30 mcg/0.5 mL **Rebif:** Single-dose autoinjector or prefilled syringe: 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, 44 mcg/0.5 mL
Interferon beta-1b (Betaseron, Extavia)	Single-use vial: 0.3 mg
Glatiramer Acetate (Copaxone, Glatopa)	Single-dose, prefilled syringe: 20 mg/mL, 40 mg/mL
Peginterferon beta-1a (Plegridy)	For SC administration - single-dose prefilled pen or syringe: 63 mcg/0.5 mL, 94 mcg/0.5 mL, 125 mcg/0.5 mL For IM administration - single-dose prefilled syringe: 125 mcg/0.5 mL

Drug	Availability
Teriflunomide (Aubagio)	Tablets: 7 mg, 14 mg
Cladribine (Mavenclad)	Tablet: 10 mg
Siponimod (Mayzent)	Tablets: 0.25 mg, 2 mg
Alemtuzumab (Lemtrada)	Single-use vial: 12 mg/1.2 mL
Mitoxantrone (Novantrone)	Multidose vial: 20 mg/10 mL, 25 mg/12.5 mL, 30 mg/15 mL
Ocrelizumab (Ocrevus)	Single-dose vial: 300 mg/10 mL
Natalizumab (Tysabri)	Single-use vial: 300 mg/15 mL
Diroximel Fumarate (Vumerity)	Delayed-release capsules: 231 mg
Monomethyl fumarate (Bafiertam)	Delayed-release capsule: 95 mg
Ozanimod (Zeposia)	Capsules: 0.23 mg, 0.46 mg, 0.92 mg
Ofatumumab (Kesimpta)	Single-dose prefilled Sensoready pens and prefilled syringes: 20 mg/0.4 mL

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Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1826	Injection, interferon beta-1a, 30 mcg
Q3027	Injection, interferon beta-1a, 1 mcg for intramuscular use
Q3028	Injection, interferon beta-1a, 1 mcg for subcutaneous use
J1830	Injection interferon beta-1b, 0.25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1595	Injection, glatiramer acetate, 20 mg
J0202	Injection, alemtuzumab, 1 mg
J9293	Injection, mitoxantrone HCl, per 5 mg
J2323	Injection, natalizumab, 1 mg
J9302	Injection, ofatumumab, 10 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	11.20.19	11.19
1Q 2020 annual review: added Vumerity for diagnosis of CIS, RRMS, and SPMS; starting and references reviewed and updated	01.14.20	01.20
Added requirements for documentation of baseline relapses/EDSS and objective measures of positive response upon re-authorization; Added EDSS table; Modified continued approval duration to 6 months for the first re-authorization and 12 months for second/subsequent re-authorizations; Added re-direction to the Novantrone policy CP.PHAR.258 if request is for diagnoses other than RRMS and SPMS; Added re-direction to the AZ.CP.PHAR.06 Cytokine and CAM Antagonists policy if Tysabri for Crohn's Disease; added Bafiertam (pending FDA approval) and Zeposia for diagnosis of CIS, RRMS, and SPMS; added Appendix B: Therapeutic Alternatives; added Coding Implications; Lemtrada: clarified that only 1 treatment course may be approved per authorization; Mavenclad: clarified that only 1 treatment course may be approved per authorization and 2 courses lifetime total; references reviewed and updated.	04.11.20	04.20
For Bafiretam- Drug is now FDA approved - criteria and reference updated per FDA labeling;	7.7.20	07.20
RT2: added new subcutaneous dosage form Kesimpta to the policy for the treatment of multiple sclerosis. Added list of AHCCCS preferred/non-preferred drugs; Updated format to break down by drug; For Betaseron and Rebif requests, removed the following criteria: failure of one of the following at up to maximally indicated doses, unless contraindicated or clinically significant adverse	02.12.21	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
effects are experienced: glatiramer (Copaxone 20 mg or Glatopa 40 mg) or Gilenya, AND Avonex; For SPMS for Extavia, Aubagio, Bafiertam, Mayzent, Plegridy, Tecfidera, Vumerity, Zeposia, Mavenclad, Novantrone, Ocrevus, and Tysabri, removed criteria for failure of the preferred disease modifying therapies for MS such as glatiramer (Copaxone 20 mg or Glatopa 40 mg), Gilenya, an interferon-beta agent (Avonex®, Betaseron®, Rebif®); references reviewed and updated.		
2Q 2021 annual review: no significant changes; RT4: added new IM dosage form and updated Dosing and Administration to indicate that Plegridy can be administered SC or IM; Aubagio, Lemtrada: updated Appendix C with additional contraindications per revised PI; Tecfidera, Vumerity, Bafiertam: updated Appendix C; Avonex: updated Appendix C to indicate the albumin contraindication only applies to the vial for Avonex per revised PI; removed Avonex vial per PI	04.14.21	05.21
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21
Per November SDC- not able to add recommendations for Extavia. References updated for Betaseron and Extavia.	01.29.22	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.