PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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MULTIPLE SCLEROSIS INJECTABLE THERAPY:
AVONEX® (interferon beta-1a)
BETASERON® (interferon beta-1b)
COPAXONE® (glatiramer acetate)
EXTAVIA® (interferon beta-1b)
Glatiramer Acetate
GLATOPA® (glatiramer acetate)
KESIMPTA® (ofatumumab)
PLEGRIDY™ (peginterferon beta-1a)
REBIF® (interferon beta-1a)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

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All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Interferons and Glatiramer

Criteria:

- **Criteria for initial therapy:** Avonex, Betaseron, Copaxone, Extavia, glatiramer acetate, Glatopa, Plegridy, and Rebif is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of a relapsing form of multiple sclerosis (MS), to include clinically isolated syndrome (experienced first clinical episode and has MRI features consistent with MS), relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS)
  4. Individual has an Expanded Disability Status Scale (EDDS) score of less than or equal to 5.5
  5. There are no significant interacting drugs
  6. Requested treatment is not to be used concurrently with other injectable MS agent or oral MS medications (e.g., Aubagio (teriflunomide), Gilenya (fingolimod), Mayzent (siponimod), Tecfidera (dimethyl fumarate), etc., except for Ampyra (dalfampridine), which is intended to improve walking speed rather than disease progression)
  7. For **glatiramer acetate** and **Glatopa** only: Individual has failure (a trial of at least 4 weeks), contraindication or intolerance to brand Copaxone

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Avonex, Betaseron, Copaxone, Extavia, glatiramer acetate, Glatopa, Plegridy, and Rebif is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

2. Individual's condition responded while on therapy
    a. Response is defined as achieves and maintains **THREE** of the following:
        i. Mild/minimal to no functional neurologic (pyramidal, cerebellar, brainstem, sensory) disabilities
        ii. Ambulatory without need for assistance
        iii. Reduction in number of exacerbations or relapses of MS
        iv. Prolonged time to exacerbation or relapses of MS
        v. Reduction in hospitalizations for MS
        vi. There is no evidence of disease progression

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Hepatic injury such as liver failure, hepatitis with jaundice
        ii. With interferon therapy:
            1. Depression, suicide, and psychotic disorders
            2. Thrombotic Microangiopathy
            3. New autoimmune disorder
            4. Seizure
            5. Worsening of congestive heart failure

5. There are no significant interacting drugs

6. Requested treatment is not to be used concurrently with other MS injectable or oral MS medications (e.g., Aubagio (teriflunomide), Gilenya (fingolimod), Mayzent (siponimod), Tecfidera (dimethyl fumarate), etc., except for Ampyra (dalfampridine), which is intended to improve walking speed rather than disease progression)

Renewal duration: 12 months

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

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

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

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KESIMPTA (ofatumumab)

Criteria:

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

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of a relapsing form of multiple sclerosis (MS), to include clinically isolated syndrome (experienced first clinical episode and has MRI features consistent with MS), relapsing-remitting MS (RRMS) and active secondary progressive MS (SPMS)
4. Individual has **ONE** of the following:
    a. Had at least one relapse in the previous year
    b. Had two relapses in the previous 2 years
    c. There is a T1 gadolinium-enhancing (GdE) lesion in the previous year
5. Individual has an Expanded Disability Status Scale (EDDS) score of less than or equal to 5.5
6. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Screening for hepatitis B infection (HBV)
    b. Testing for quantitative serum immunoglobulins
7. Has a failure, contraindication per FDA label, or intolerance to two or more drugs indicated for the treatment of relapsing forms of multiple sclerosis (such as Tecfidera (dimethyl fumarate), Aubagio (teriflunomide), Gilenya (fingolimod), Copaxone (glatiramer), or interferons such as, Rebif, Betaseron, Intron A, Intron B)
8. There are **NO** FDA-label contraindications, such as:
    a. Active hepatitis B virus (HBV) infection
9. Any required vaccinations (with live, live-attenuated, or inactive vaccines) are administered before starting Kesimpta (ofatumumab)
10. There are no significant interacting drugs
11. Requested treatment is not to be used concurrently with other injectable MS agent or oral MS medications (e.g., Aubagio (teriflunomide), Gilenya (fingolimod), Mayzent (siponimod), Tecfidera (dimethyl fumarate), etc., except for Ampyra (dalfampridine), which is intended to improve walking speed rather than disease progression)

Initial approval duration: 6 months

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

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

  2. Individual's condition responded while on therapy
     a. Response is defined as achieves and maintains **THREE** of the following:
        i. Mild/minimal to no functional neurologic (pyramidal, cerebellar, brainstem, sensory) disabilities
        ii. Ambulatory without need for assistance
        iii. Reduction in number of exacerbations or relapses of MS
        iv. Prolonged time to exacerbation or relapses of MS
        v. Reduction in hospitalizations for MS
        vi. There is no evidence of disease progression

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
     a. Contraindications as listed in the criteria for initial therapy section
     b. Significant adverse effect such as:
        i. Serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins
        ii. Progressive multifocal leukoencephalopathy

  5. Vaccinations (with live, live-attenuated, or inactive vaccines) are not planned during Kesimpta (ofatumumab) use

  6. There are no significant interacting drugs

  7. Requested treatment is not to be used concurrently with other MS injectable or oral MS medications (e.g., Aubagio (teriflunomide), Gilenya (fingolimod), Mayzent (siponimod), Tecfidera (dimethyl fumarate), etc., except for Ampyra (dalfampridine), which is intended to improve walking speed rather than disease progression)

  Renewal duration: 12 months

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

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

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

MULTIPLE SCLEROSIS INJECTABLE THERAPY

Description:

Multiple sclerosis (MS) is an unpredictable and potentially disabling disease of the central nervous system, which interrupts the flow of information within the brain, and between the brain and body. The disease is thought to be triggered in a genetically susceptible individual by a combination of one or more environmental factors. In MS, the immune system attacks tissue and cells within the central nervous system (CNS) and causes damage to nerve connections resulting in neurological symptoms. Although MS is not curable, there is much an individual can do to manage the disease and symptoms it can cause. A number of medications have been shown to modify or slow the course of MS.

Because MS can affect any area of the brain, optic nerve, or spinal cord, MS can cause almost any neurologic symptom. Patients typically present as young adults with 2 or more clinically distinct episodes of CNS dysfunction with at least partial resolution. Typical episodes involve numbness, weakness, or dyscoordination affecting an arm, a leg, or both. Additional symptoms include pain, vertigo, cognitive deficits (e.g., impaired memory, attention, or judgment), fatigue, speech deficits (e.g., dysarthria or less commonly aphasia), and bowel, bladder, and sexual dysfunction.

The pathological hallmark of MS is the cerebral or spinal plaque seen on magnetic resonance imaging (MRI). Plaques are discrete regions of demyelination with relative preservation of axons. However, the basis of the diagnosis remains the neurologic history and physical examination. Original diagnostic criteria required symptoms and signs disseminated in time and space (i.e., more than one episode involving more than one area of the CNS). These criteria have been largely replaced by the McDonald criteria, developed in 2001 by the International Panel on the Diagnosis of Multiple Sclerosis. The McDonald criteria retain many features of the original diagnostic criteria and are intended for use in both clinical practice and clinical trial settings. Diagnoses of “definite MS,” “possible MS,” or, if there is a better explanation for the clinical presentation, “not MS” are determined by findings on clinical exam, MRI, cerebrospinal fluid, and visual evoked potentials. The term “clinically isolated syndrome” (CIS) describes patients who have suffered a first clinical attack but do not meet diagnostic criteria for definite MS. The McDonald criteria were updated in 2010 and allows the diagnosis of MS in some patients with CIS.

There are four recognized clinical forms of MS: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS). RRMS is the most common form of the disease. As the understanding of the disease process in MS advances, the definitions have evolved:

Definitions:

National Multiple Sclerosis Society 1996 Disease-Course Definitions:

- Primary Progressive (PPMS):
  PPMS is characterized by steady worsening of neurologic functioning, without any distinct relapses (also called attacks or exacerbations) or periods of remission. Rate of progression may vary over time with occasional plateaus or temporary improvement but the progression is continuous.

- Progressive-Relapsing (PRMS):
  PRMS is the least common of the four disease courses. Similar to PPMS, individuals with PRMS experience steadily worsening neurologic function and disease progression from the very beginning, in addition to occasional relapses like those experienced with RRMS. Because PRMS is progressive from onset, it may be

initially diagnosed as PPMS, and then subsequently changed to PRMS when a relapse occurs. Although this disease course is progressive from the outset, each individual's symptoms and rate of progression will be different.

- Relapsing-Remitting (RRMS):
  RRMS is characterized by clearly defined attacks of worsening neurologic function. These attacks, often called relapses, flare-ups or exacerbations, are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease. RRMS is the most common disease course at the time of diagnosis. Approximately 85 percent of individuals are initially diagnosed with RRMS, compared to 10-15 percent with progressive forms of the disease.

- Secondary Progressive (SPMS):
  SPMS follows after the relapsing-remitting disease course (RRMS). Of the 85 percent of individuals who are initially diagnosed with RRMS, most will eventually transition to SPMS, which means that after a period of time in which they experience relapses and remissions, the disease will begin to progress more steadily (although not necessarily more quickly), with or without any relapses (also called attacks or exacerbations).

National Multiple Sclerosis Society 2013 Disease-Course Revisions:

- Clinically Isolated Syndrome (CIS):
  CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS.

- Relapsing-Remitting (RRMS):
  RRMS is characterized by clearly defined attacks of new or worsening neurologic function. These attacks, often called relapses, flare-ups or exacerbations, are followed by partial or complete recovery periods (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. Approximately 85 percent of people with MS are initially diagnosed with RRMS.

- Primary Progressive (PPMS):
  PPMS is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. Approximately 15 percent of people with MS are diagnosed with PPMS.

- Secondary Progressive (SPMS):
  SPMS follows after the relapsing-remitting disease course (RRMS). Most individuals who are diagnosed with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function (accumulation of disability) over time.

McDonald criteria:

Clinical Presentation	Additional Data Needed
* 2 or more attacks (relapses) * 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
* 2 or more attacks * 1 objective clinical lesion	Dissemination in space, demonstrated by: * MRI

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	* **or** a positive CSF and 2 or more MRI lesions consistent with MS * **or** further clinical attack involving different site
* 1 attack * 2 or more objective clinical lesions	Dissemination in time, demonstrated by: * MRI * **or** second clinical attack
* 1 attack * 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: * MRI * **or** positive CSF and 2 or more MRI lesions consistent with MS **and** Dissemination in time demonstrated by: * MRI * **or** second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) **and** Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF

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

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

Expanded Disability Status Scale (EDSS) steps of 1.0-4.5 refer to people with MS who are fully ambulatory. EDSS steps of 5.0-9.5 are defined by the impairment to ambulation.

Kurtzke Expanded Disability Status Scale	
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others

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4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self-care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

Resources:

Avonex (interferon beta-1a) product information, revised by Biogen Inc. 03-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Betaseron (interferon beta-1b) product information, revised by Bayer HealthCare Pharmaceuticals Inc. 03-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Copaxone (glatiramer acetate) product information, revised by Teva Neuroscience Inc. 07-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Extavia (interferon bta-1b) product information, revised by Novartis Pharmaceuticals Corporation 10-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Glatiramer acetate product information, revised by Mylan Pharmaceuticals Inc. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

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Glatopa (glatiramer acetate) product information, revised by Sandoz Inc. 07-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Kesimpta (ofatumumab) product information, revised by Novartis Pharmaceuticals Corporation 08-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Plegridy (peginterferon beta-1a) product information, revised by Biogen Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Rebif (interferon beta-1a) product information, revised by EMD Serono Inc. 08-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 27, 2021.

Olek MJ, Mowry E. Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 27, 2021.

Olek MJ, Mowry E. Treatment of primary progressive multiple sclerosis in adults. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 27, 2021.

Olek MJ, Mowry E. Treatment of secondary progressive multiple sclerosis in adults. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 27, 2021.

Olek MJ, Howard J. Management of clinically and radiologically isolated syndromes suggestive of multiple sclerosis. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 27, 2021.

Olek MJ, Howard J. Treatment of acute exacerbations of multiple sclerosis in adults. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 27, 2021.