BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 4/01/2019**
SECTION: DRUGS	**LAST REVIEW DATE: 8/20/2020**
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MULTIPLE SCLEROSIS INJECTABLE THERAPY:
AVONEX® (interferon beta-1a)
BETASERON® (interferon beta-1b)
COPAXONE® (glatiramer acetate)
EXTAVIA® (interferon beta-1b)
GLATIRAMER (glatiramer acetate)
GLATOPA® (glatiramer acetate)
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.**

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 **ONE** of the following:
     a. Individual has a relapsing form of multiple sclerosis, **EITHER** of the following:
        i. Relapsing-remitting MS (RRMS)
        ii. Secondary progressive MS (SPMS)
        iii. Progressive-Relapsing MS (PRMS)
     b. Individual has experienced a first clinical episode and has MRI features consistent with multiple sclerosis

  4. There are **NO** contraindications

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

  6. For **glatiramer acetate** and **Glatopa** only: Individual has failure (a trial of at least 4 weeks), contraindication or intolerance to Copaxone

  Initial approval duration: 6 months

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- **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:

  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 unacceptable adverse drug effects that may exclude continued use

  5. There are no significant interacting drugs

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

  Renewal duration: 12 months

- Avonex, Betaseron, Copaxone, Extavia, glatiramer acetate, Glatopa, Plegridy, and Rebif for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any one or more of the following criteria are met:

  1. Lack of final approval from the Food and Drug Administration;
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes;
  3. Insufficient evidence to support improvement of the net health outcome;
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; **or**
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, but are not limited to:
  - Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration.

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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:

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.

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- 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.

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Definitions:

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 * **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

Resources:

UpToDate: Disease-modifying treatment of relapsing-remitting multiple sclerosis in adults. Current through Nov 2018

National Multiple Sclerosis Society. Primary-Progressive Multiple Sclerosis (PPMS). Accessed 03/18/2017, 08/02/2016.

National Multiple Sclerosis Society. Progressive-Relapsing Multiple Sclerosis (PRMS). Accessed 03/18/2017, 09/11/2014.

National Multiple Sclerosis Society. Relapsing-Remitting Multiple Sclerosis (RRMS). Accessed 03/18/2017, 08/02/2016.

National Multiple Sclerosis Society. Secondary-Progressive Multiple Sclerosis (SPMS). Accessed 03/18/2017, 08/02/2016.

National Multiple Sclerosis Society. Clinically Isolated Syndrome (CIS). Accessed 03/18/2017, 08/01/2016.

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National Multiple Sclerosis Society. Just the Facts. Accessed 03/18/2017, 08/01/2016.

McDonald WI, Compston A, Edan G, et al.: Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001; 50 (1):121-127

Polman CH, Reingold SC, Edan G, et al.: Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria." Ann Neurol 2005; 58 (6):840-846

Polman CH, Reingold SC, Banwell B, et al.: 2010 Revisions to the McDonald Criteria. Ann Neurol 2011; 69 (2):292-302.