BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINE

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)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

INTERFERONS AND GLATIRAMER

ORIGINAL EFFECTIVE DATE: 04/01/2019 | ARCHIVE DATE: | LAST REVIEW DATE: 11/20/2025 | LAST CRITERIA REVISION DATE: 11/21/2024

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- **Criteria for initial therapy:** Avonex, Betaseron, Copaxone, Extavia, glatiramer acetate, Glatopa, Plegridy, and Rebif are 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. Individual has a confirmed diagnosis of a relapsing form of multiple sclerosis (MS) including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease with **BOTH** of the following:
     a. Clinical symptoms or attack consistent with demyelinating disease
     b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:
        i. MRI is definitive for MS diagnosis
        ii. If an MRI is not definitive for MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

  4. **For brand Copaxone:** Individual has failure (after at least 6-month trial), contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following: [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)
     a. Glatopa (glatiramer)
     b. Glatiramer

  5. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Avonex, Betaseron, Copaxone, Extavia, glatiramer acetate, Glatopa, Plegridy, and Rebif are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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

  2. Individual has documentation of positive clinical response to therapy defined as achieves and maintains **TWO** of the following:
     a. Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc.)
     b. Reduction in number of exacerbations or relapses of MS
     c. Reduction in use of high dose steroids or hospitalizations for MS

  3. Individual has been adherent with the medication

  4. **For brand Copaxone:** Individual has failure (after at least 6-month trial), contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following: [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

a. Glatopa (glatiramer)
b. Glatiramer

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Hepatic injury such as liver failure, hepatitis with jaundice
    b. With Interferon therapy:
        i. Depression, suicide, ad psychotic disorders
        ii. Thrombotic Microangiopathy
        iii. New autoimmune disorder
        iv. Seizure
        v. Worsening of congestive heart failure
        vi. Drug-induced lupus erythematosus
        vii. Pulmonary arterial hypertension

6. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

Renewal duration: 12 months

- If criteria for response to therapy is not met, consider changing disease modifying therapy

- 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 Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

KESIMPTA (ofatumumab)

- **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. Individual has a confirmed diagnosis of a relapsing form of multiple sclerosis (MS) including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease with **BOTH** of the following:
    a. Clinical symptoms or attack consistent with demyelinating disease
    b. MRI of the brain and/or spinal cord was performed and meets **ONE** of the following:
        i. MRI is definitive for MS diagnosis

ii. If an MRI is not definitive for MS, a CSF evaluation was done and demonstrates CSF-specific oligoclonal bands consistent with MS

4. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. Completion of any necessary immunizations according to current immunization guidelines 4 weeks prior to initiation
    b. Evidence of testing for hepatitis B infection prior to initiation of therapy
    c. Serum immunoglobulin levels
    d. No evidence of active infections or uncontrolled infections

5. There are **NO** FDA-label contraindications, including active hepatitis B virus (HBV) infection, confirmed by positive results for hepatitis B surface antigen and anti-HBV tests

6. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Kesimpta (ofatumumab) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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

2. Individual has documentation of positive clinical response to therapy defined as achieves and maintains **TWO** of the following:
    a. Stabilization or reduction in disease activity as evaluated by MRI (decrease in gadolinium enhancing lesions, decrease in number of new or enlarging T2 lesions, etc)
    b. Reduction in number of exacerbations or relapses of MS
    c. Reduction in use of high dose steroids or hospitalizations for MS

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 as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effects 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. Requested treatment will not be used concurrently with other multiple sclerosis disease-modifying therapy (see Definitions section) or other immunomodulatory, immunosuppressive or myelosuppressive therapy for other conditions.

Renewal duration: 12 months

- If criteria for response to therapy is not met, consider changing disease modifying therapy

- 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 Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

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 2017 and allows the diagnosis of MS in some patients with CIS.

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There are four recognized clinical forms of MS: clinically isolated syndrome (CIS), relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). RRMS is the most common form of the disease.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

MS attack/exacerbation/relapse episode:
A monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or sub-acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonymous.

Pseudorelapse:
Temporary worsening of existing MS symptoms caused by increased body temperature, underlying infection, metabolic disturbance, or medical illness.

Stages or subtypes of Multiple Sclerosis:

- Clinically Isolated Syndrome (CIS):
  CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system and is suggestive of MS. The episode, by definition must last for at least 24 hours, is characteristic of MS 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. CIS symptoms develop over a course of hours to days and then decline over weeks to months and the remission may not be complete. CIS is an isolated attack in time (not necessarily isolated in space) and is a potential precursor to MS.

  The diagnosis of MS can be made for some individuals at the time of presentation of a first clinical attack of CIS if a single MRI obtained at any time shows dissemination in space and evidence for dissemination in time showing simultaneous presence of gadolinium-enhancing and non-enhancing lesions, **or** (as a substitute for dissemination in time) by the presence of cerebrospinal fluid-specific oligoclonal bands.

- Radiological Isolated Syndrome (RIS):
  RIS is defined by incidental MRI findings that are highly suggestive of MS, based upon location and morphology within the central nervous system, in an asymptomatic patient lacking any history, symptoms, or signs of demyelination. The MRI by definition was obtained for a completely unrelated condition.

- Relapsing-Remitting (RRMS):
  RRMS is characterized by clearly defined attacks (relapses, flare-ups or exacerbations), followed by full recover or with sequelae and residual deficit on recovery. There is no or minimal disease progression during periods between relapses. Individual relapses may result in severe residual disability. Approximately 85 percent of people with MS are initially diagnosed with RRMS and most will eventually enter a secondary progressive phase.

- Secondary Progressive (SPMS):

SPMS follows after the relapsing-remitting disease. Most individuals who are diagnosed with RRMS will eventually transition to SPMS in which there is a steady worsening of neurologic function (accumulation of disability) with or without superimposed attacks. At this stage, there is a reduction in relapse rate and new lesions are less common (so-called immunosenescence) but progressive (disability) MS increases. This type of MS causes the greatest amount of neurologic disability from MS.

- Primary Progressive (PPMS):
  PPMS is characterized by disease progression (accumulation of disability) from the onset of symptoms, with occasional plateaus, temporary minor improvements; acute relapses may occur.

Disease activity and progression:

- Activity is determined by clinical relapses or MRI evidence of contrast enhancing lesions and/or new or unequivocally enlarging T2 lesions
- Progression is a measure of disability, and it is independently quantified from relapses; it is characteristic of PPMS and SPMS
- Progressive disease (PPMS and SPMS) can be characterized as one of the following:
  - Active and with progression
  - Active without progression
  - Not active but with progression
  - Not active and without progression (stable disease)

Most Common Clinical Symptoms of MS attack (wide range of symptoms affecting different parts of the body):

- Unilateral optic neuritis (loss or reduction of vision in 1 eye with painful eye movements)
- Diplopia
- Ascending sensory disturbance and/or weakness
- Altered sensation or pain travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's sign)
- Progressive difficulties with balance and gait

McDonald criteria, 2017:

# Clinical attacks	# Lesions with objective clinical evidence	Additional data needed for a diagnosis of MS
2 or more	2 or more	None[a]
	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location[b])	None[a]
	1	**Dissemination in space** demonstrated by an additional attack implicating a different CNS site by MRI
1	2 or more	**Dissemination in time** demonstrated by an additional clinical attack or by MRI **OR** demonstration of CSF-specific oligoclonal bands[c]

	1	**<u>Dissemination in space</u>** demonstrated by an additional clinical attack implicating a different CNS site or by MRI ***AND*** **<u>Dissemination in time</u>** demonstrated by an additional clinical attack or by MRI **OR** demonstration of CSF-specific oligoclonal bands[c]
a: No additional tests are required to demonstrate dissemination in space and time; however, a brain MRI should be obtained in all individuals in whom a diagnosis of MS is being considered		
b: Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings.		
c: The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure		
Criteria for Dissemination in Space		

Dissemination in space is defined as the development of lesions in distinct anatomic locations within the central nervous system, indicating a multifocal process.
 	
The McDonald criteria for dissemination in space are fulfilled if **one** of the following is present in a patient with a CIS or typical MS attack:
• An MRI with *one or more hyperintense T2 lesions* that are *characteristic of MS* in at least **<u>two</u>** <u>of four MS-typical regions of the central nervous system</u>:
  ○ Periventricular
  ○ Cortical or juxtacortical
  ○ Infratentorial
  ○ Spinal cord
• Development of an additional clinical attack characteristic of MS, supported by objective clinical evidence, that implicates a different central nervous system site		

Criteria for Dissemination in Time		
Dissemination in time requires the development or appearance of new central nervous system lesions over time. The McDonald criteria for dissemination in time are fulfilled if **one** of the following is present in a patient with a CIS or a characteristic MS attack: • The development of an additional clinical attack, supported by objective clinical evidence, that is characteristic of MS • An MRI of the brain and/or spinal cord with the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, or by a new hyperintense T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan • Finding of cerebrospinal fluid-specific oligoclonal bands (as a substitute for dissemination in time)		

Disease Modifying Therapy Options:

- Oral Medications:
  - Cladribine (Mavenclad)
  - Fumarates:
    - Dimethyl Fumarate (Tecfidera and generic)
    - Diroximel fumarate (Vumerity)
    - Monomethyl fumarate (Bafiertam)

- Sphingosine-1-phosphate (S1P) receptor modulators
  - Fingolimod (Gilenya and generic, Tascenso ODT)
  - Ozanimod (Zeposia)
  - Ponesimod (Ponvory)
  - Siponimod (Mayzent)
- Teriflunomide (Aubagio and generic)

- Injectable Medications:
  - Interferon beta-1a (Avonex (IM), Plegridy (SQ), Rebif (SQ))
  - Interferon beta-1b (Betaseron (SQ), Extavia (SQ))
  - Glatiramer acetate (Copaxone (SQ), and generic, Glatopa (SQ))
  - Monoclonal antibody Mediations:
    - Alemtuzumab (Lemtrada IV)
    - Natalizumab (Tysabri IV)
    - Ocrelizumab (Ocrevus IV)
    - Ofatumumab (Kesimpta SQ)
    - Ublituximab (Briumvi IV)

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
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. 07-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Betaseron (interferon beta-1b) product information, revised by Bayer HealthCare Pharmaceuticals Inc. 07-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Copaxone (glatiramer acetate) product information, revised by Teva Neuroscience Inc. 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Extavia (interferon beta-1b) product information, revised by Novartis Pharmaceuticals Corporation 05-2016. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Glatiramer acetate product information, revised by Mylan Pharmaceuticals Inc. 02-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Glatopa (glatiramer acetate) product information, revised by Sandoz Inc. 02-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Kesimpta (ofatumumab) product information, revised by Novartis Pharmaceuticals Corporation 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Plegridy (peginterferon beta-1a) product information, revised by Biogen Inc. 07-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Rebif (interferon beta-1a) product information, revised by EMD Serono Inc. 07-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

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Olek MJ, Mowry E. Overview of disease-modifying therapies for multiple sclerosis. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic updated April 28, 2025. Accessed September 03, 2025.

Olek MJ, Howard J. Treatment of acute exacerbations of multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated May 27, 2025. Accessed September 03, 2025.

Olek MJ, Mowry E. Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic updated January 10, 2025. Accessed September 03, 2025.

Olek MJ, Mowry E. Treatment of primary progressive multiple sclerosis in adults. In: UpToDate, González-Scarano F, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic updated January 10, 2025. Accessed September 03, 2025.

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