LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.644

Medical Pharmacologic Treatment of Multiple Sclerosis

Effective Date:	Feb. 1, 2025	RELATED MEDICAL POLICIES:	
Last Revised:	Jan. 14, 2025	5.01.556	Rituximab: Non-oncologic and Miscellaneous Uses
Replaces:	N/A	5.01.565	Pharmacotherapy of Multiple Sclerosis
		11.01.523	Site of Service: Infusion Drugs and Biologic Agents

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only.

Site of Service *and* the infusion drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Multiple sclerosis is a disease that occurs when the body's immune system reacts to and damages nerve cells. Damage occurs to nerves and their connections in the brain and spinal cord. Multiple sclerosis is also called MS. People with MS can have a variety of symptoms including vision problems, numbness and tingling, muscle weakness and other problems. Some people have only a few symptoms, and others may be severely disabled form the disease. There are several types of MS as well. This policy discusses the medical drugs used to treat MS and which of those drugs need to be pre-approved by the health plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a

service may be covered.

Policy Coverage Criteria

Site of Service Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Briumvi (ublituximab-xiiy)
- Ocrevus (ocrelizumab)
- Tyruko (natalizumab-sztn)
- Tysabri (natalizumab)

Site of Service Administration	Medical Necessity (Applies to all Plans)
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.**

Site of Service Administration	Medical Necessity (Applies to all Plans)
• **Hospital-based outpatient clinical level of care**	**This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug

Site of Service Administration	Medical Necessity (Applies to all Plans)

	This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:
	• CRS is grade 3 or 4 as evidenced by ALL the following:
	  ○ Temperature greater or equal to 38 °C
	  ○ Hypotension that requires one or more vasopressors
	  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)
	AND
	• The individual will be admitted into an inpatient setting as soon as possible

Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Note: This policy does not address intravenous (IV) and injectable therapy services for individual's receiving inpatient services.

Drug	Medical Necessity
Anti-CD52 • **Lemtrada (alemtuzumab) IV**	**Lemtrada (alemtuzumab) may be considered medically necessary for the treatment of relapsing forms of multiple sclerosis, including relapsing-remitting disease and active secondary progressive disease, when the following conditions are met:** • The individual is aged 17 years or older **AND** • Lemtrada (alemtuzumab) is not used concurrently with other MS disease modifying drugs **AND**

Drug	Medical Necessity
	• Has had an inadequate response to two or more disease modifying drugs indicated for the treatment of multiple sclerosis (any two of the following: B-interferon(s), dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer, monomethyl fumarate, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, siponimod or teriflunomide) **AND** • Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis
α4 Integrin Inhibitors • **Tyruko (natalizumab-sztn) IV** • **Tysabri (natalizumab) IV**	**Tyruko (natalizumab-sztn) and Tysabri (natalizumab) are subject to review for site of service administration.** **Tyruko (natalizumab-sztn) and Tysabri (natalizumab) may be considered medically necessary for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following conditions are met:** • The individual is aged 18 years or older **AND** • Must have an expanded disability status score (**EDSS**) of less than 6 **AND** • The medication is not used concurrently with other MS disease modifying drugs **AND** • Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis **Note:** Due to safety concerns, access to Tysabri requires enrollment in the TOUCH registry maintained by the manufacturer (see **https://www.touchprogram.com/TTP/**) and Tyruko requires enrollment in the Tyruko REMS program.
CD20-directed cytolytic antibody	**Briumvi (ublituximab-xiiy) is subject to review for site of service administration.**

Drug	Medical Necessity
• **Briumvi (ublituximab-xiiy) IV**	**Briumvi (ublituximab-xiiy) may be considered medically necessary for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following conditions are met:** • The individual is aged 18 years or older **AND** • Must have an expanded disability status score (**EDSS**) of less than 6 **AND** • Briumvi (ublituximab-xiiy) is not used concurrently with other MS disease modifying drugs **AND** • Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis
CD20-directed cytolytic antibody • **Ocrevus (ocrelizumab) IV**	**Ocrevus (ocrelizumab) is subject to review for site of service administration.** **Ocrevus (ocrelizumab) may be considered medically necessary for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following conditions are met:** • The individual is aged 18 years or older **AND** • Must have an expanded disability status score (**EDSS**) of less than 6 **AND** • Ocrevus (ocrelizumab) is not used concurrently with other MS disease modifying drugs **AND** • Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis

Drug	Medical Necessity
	Ocrevus (ocrelizumab) may be considered medically necessary for the treatment of primary progressive multiple sclerosis when the following conditions are met: • The individual is aged 18 years or older **AND** • Must have an expanded disability status score (**EDSS**) of less than 7 **AND** • Ocrevus (ocrelizumab) is not used concurrently with other MS disease modifying drugs **AND** • Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis
CD20-directed cytolytic antibody • **Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) SC**	**Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) may be considered medically necessary for the treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following conditions are met:** • The individual is aged 18 years or older **AND** • Must have an expanded disability status score (**EDSS**) of less than 6 **AND** • Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) is not used concurrently with other MS disease modifying drugs **AND** • Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis **Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) may be considered medically necessary for the treatment of primary progressive multiple sclerosis when the following conditions are met:** • The individual is aged 18 years or older

Drug	Medical Necessity
	AND • Must have an expanded disability status score (**EDSS**) of less than 7 **AND** • Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) is not used concurrently with other MS disease modifying drugs **AND** • Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of the medications listed in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews and all other reviews for all drugs listed in policy may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J0202	Injection, alemtuzumab (Lemtrada), 1 mg
J2323	Injection, natalizumab (Tysabri), 1mg
J2329	Injection, ublituximab-xiiy (Briumvi), 1mg
J2350	Injection, ocrelizumab (Ocrevus), 1 mg
J3590	Unclassified biologics (used to report Ocrevus Zunovo)
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar (Tyruko), 1 mg (new code effective 04/01/2024)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

The age described in this policy for Site of Service reviews for medical necessity is 13 years of age or older. The age criterion is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatric unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Benefit Application

The medications listed in this policy are managed through the medical benefit.

Evidence Review

It is currently thought that multiple sclerosis (MS) is the result of a combination of factors including immune response, genetics, infection, and environmental issues. MS is characterized by the destruction of the myelin sheath that surrounds axons of the central nervous system (CNS) and eventual axonal damage. This is believed to be an autoimmune attack against myelin and the myelin-producing oligodendrocytes. There is an associated inflammatory response involving B-cells, T-cells, macrophages, antibodies, and complement. The myelin sheath is replaced by sclerotic plaques. The damage to the myelin sheath can delay or halt nerve impulses. Axonal damage leads to loss of nerve impulses.

An estimated 250,000 to 400,000 cases exist in the United States (US). In 2000, the estimated prevalence was 191/100,000 Caucasians in the US, with an incidence rate of 7.3/100,000 person-years at risk. Diagnosis usually occurs when individuals are between 20 and 50 years of age. The disease is more prevalent: 1) further away from the equator; 2) in Caucasians; and 3) in women. Other risk factors include Epstein-Barr virus exposure, vitamin D deficiency, and smoking.

MS usually follows one of the following four disease courses, but individual presentation can vary quite widely.

1. Relapsing-remitting MS (RRMS): clearly defined acute attacks followed by periods of partial or full recovery. This is the most common course of the disease describing approximately 85% of MS individuals.
2. Primary-progressive MS (PPMS): the disease steadily progresses although there may be occasional plateaus or remissions. The individual does not experience acute attacks. Approximately 10% of MS individuals have PPMS.
3. Secondary-progressive MS (SPMS): often follows RRMS. Individual experiences acute attacks similar to RRMS, but with progressively less recovery after acute attacks and progressively worsening function between attacks. As with PPMS, there may be occasional plateaus or remissions.

Progressive-relapsing MS (PRMS): initially presents as PPMS with steady disease progression, but later experiences acute attacks followed by partial recovery. This is only seen in approximately 5% of MS individuals.

Ocrelizumab (Ocrevus) is second-generation humanized (murine) anti-CD20 monoclonal antibody that targets $CD20^{+}$ B-lymphocytes; hence, it is an immunosuppressant. Rituximab (Rituxan) is another similar chimeric (murine/human) anti-CD20 monoclonal antibody that is used off-label for the treatment of MS. In-vitro studies suggest ocrelizumab has greater antibody-dependent cell-mediated cytotoxicity and less complement-dependent cytotoxicity compared to rituximab. Whether this is of clinical relevance remains to be established. Development of rituximab for MS was discontinued by the manufacturer given its imminent patent expiration and development of ocrelizumab ensued.

References

1. Miller AE, Rhoades RW. Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs. Curr Opin Neurology 2012;25 Suppl:S4-10.
2. Lycke J. Monoclonal antibody therapies for the treatment of relapsing-remitting multiple sclerosis: differentiating mechanisms and clinical outcomes. Ther Adv Neurol Disord. 2015;8(6):274-93.
3. Tyruko (natalizumab-sztn) prescribing information. Sandoz, Inc; Princeton, NJ. Revised August 2023.
4. Briumvi (ublituximab-xiiy) prescribing information. TG Therapeutics; Morrisville, NC. Revised December 2022.
5. Ocrevus Zunovo (ocrelizumab-hyaluronidase-ocsq) prescribing information. Genentech; South San Francisco, CA. Revised September 2024.
6. Ocrevus (ocrelizumab) prescribing information. Genentech; South San Francisco, CA. Revised June 2024.
7. Lemtrada (alemtuzumab) prescribing information. Genzyme Corporation; Cambridge, MA. Revised May 2024.
8. Tysabri (natalizumab) prescribing information. Biogen; Cambridge, MA. Revised October 2023.

History

Date	Comments
02/01/25	New policy, approved January 14, 2025. Moved Briumvi, Lemtrada, Ocrevus, Ocrevus Zunovo, Tyruko, and Tysabri from Policy 5.01.565 Pharmacotherapy of Multiple Sclerosis to this policy 5.01.644. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully insured members; only Medical

Date	Comments
	Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added a prescriber requirement and age requirement to Briumvi (ublituximab-xiiy), Lemtrada (alemtuzumab), Tysabri (natalizumab), Tyruko (natalizumab-sztn), and Ocrevus (ocrelizumab). Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.