

PHARMACY / MEDICAL POLICY – 5.01.565

Pharmacotherapy of Multiple Sclerosis


Effective Date: **July 4, 2024**
Last Revised: Mar. 12, 2024
Replaces: Extracted from
5.01.550

RELATED MEDICAL POLICIES:
5.01.556 Rituximab: Non-oncologic and Miscellaneous Uses
11.01.523 Site of Service: Infusion Drugs and Biologic Agents

*This policy has been updated.
View upcoming changes here.

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 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 from the disease. There are several types of MS as well. This policy discusses the 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 providers about when a service may be covered.

Policy Coverage Criteria

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:

- Ocrevus (ocrelizumab)
- Tysabri (natalizumab)

Site of Service Administration	Medical Necessity
<p>Medically necessary sites of service</p> <ul style="list-style-type: none"> • Physician’s office • Infusion center • Home infusion 	<p>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:</p> <ul style="list-style-type: none"> • These are the preferred medically necessary sites of service for specified drugs.
<p>Hospital-based outpatient setting</p> <ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	<p>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</p> <p>This site is considered medically necessary for the first 90 days for the following:</p> <ul style="list-style-type: none"> • The initial course of infusion of a pharmacologic or biologic agent <p>OR</p> <ul style="list-style-type: none"> • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* <p>Note: This does not include when standard dosing between infusions is 6 months or longer</p> <p>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</p>



Site of Service Administration	Medical Necessity
	<p>will travel to their home, or a hospital is the only place that offers infusions of this drug.</p> <p>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:</p> <ul style="list-style-type: none"> • 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
<p>Hospital-based outpatient setting</p> <ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	<p>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.</p>

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

Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
<p>Anti-CD52</p> <ul style="list-style-type: none"> • Lemtrada (alemtuzumab) IV 	<p>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:</p>



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<ul style="list-style-type: none"> Lemtrada (alemtuzumab) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> The individual 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)
<p>β -Interferons</p> <ul style="list-style-type: none"> Avonex, Rebif, Plegridy (Interferon-β 1a) IM/SC Betaseron, Extavia (Interferon-β 1b) SC 	<p>Interferon-β 1a or interferon-β 1b 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> β-interferons are not used concurrently with other MS disease modifying drugs
<p>Copolymers</p> <ul style="list-style-type: none"> Glatiramer SC; generic Glatopa (glatiramer) SC; generic Copaxone (glatiramer) SC; brand 	<p>Glatiramer or Glatopa (glatiramer) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Glatiramer or Glatopa (glatiramer) are not used concurrently with other MS disease modifying drugs <p>Copaxone (glatiramer) may be considered medically necessary for the treatment of relapsing forms of</p>



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<p>multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following criteria are met:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Copaxone is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> There has been documented inadequate response to or intolerance of generic glatiramer or Glatopa (glatiramer) of the same strength.
<p>Dihydroorotate Dehydrogenase Inhibitor</p> <ul style="list-style-type: none"> Aubagio (teriflunomide) Oral 	<p>Aubagio (teriflunomide) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> There has been documented inadequate response to or intolerance of generic teriflunomide <p>AND</p> <ul style="list-style-type: none"> Aubagio (teriflunomide) is not used concurrently with other MS disease modifying drugs
<p>Dihydroorotate Dehydrogenase Inhibitor</p> <ul style="list-style-type: none"> Generic teriflunomide Oral 	<p>Generic teriflunomide 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Generic teriflunomide is not used concurrently with other MS disease modifying drugs
<p>Nrf2 Pathway Activator</p> <ul style="list-style-type: none"> Bafiertam (monomethyl fumarate) Oral 	<p>Bafiertam (monomethyl fumarate) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Bafiertam (monomethyl fumarate) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> The individual had tried dimethyl fumarate first for 3 months and had an inadequate response or intolerance to dimethyl fumarate <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 380 mg per day (190 mg twice a day)
<p>Nrf2 Pathway Activator</p> <ul style="list-style-type: none"> Generic dimethyl fumarate, Oral 	<p>Generic dimethyl fumarate 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Generic dimethyl fumarate is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 480 mg per day (240 mg twice a day)



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
Nrf2 Pathway Activator <ul style="list-style-type: none"> Tecfidera (dimethyl fumarate), Oral 	<p>Tecfidera (dimethyl fumarate) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> The individual has tried generic dimethyl fumarate first for 3 months and had an inadequate response or intolerance to generic dimethyl fumarate <p>AND</p> <ul style="list-style-type: none"> Tecfidera (dimethyl fumarate) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> Dose is \leq 480 mg per day (240 mg twice a day)
Nrf2 Pathway Activator <ul style="list-style-type: none"> Vumerity (diroximel fumarate) Oral 	<p>Vumerity (diroximel fumarate) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> The individual has tried dimethyl fumarate first for 3 months and had an inadequate response or intolerance to dimethyl fumarate <p>AND</p> <ul style="list-style-type: none"> Vumerity (diroximel fumarate) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> Dose is \leq 924 mg per day (462mg twice a day)



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
Sphingosine 1-Phosphate Receptor Modulator <ul style="list-style-type: none"> • Generic fingolimod, Oral 	<p>Generic fingolimod 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:</p> <ul style="list-style-type: none"> • The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> • Medication is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> • Dose is ≤ 0.5 mg per day
Sphingosine 1-Phosphate Receptor Modulator <ul style="list-style-type: none"> • Gilenya (fingolimod) Oral • Tascenso ODT (fingolimod) 	<p>Gilenya (fingolimod) and Tascenso ODT (fingolimod) 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:</p> <ul style="list-style-type: none"> • The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> • The individual has tried generic fingolimod first and had an inadequate response or intolerance to generic fingolimod <p>AND</p> <ul style="list-style-type: none"> • Medication is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> • Dose is ≤ 0.5 mg per day
α4 Integrin Inhibitors <ul style="list-style-type: none"> • Tyruko (natalizumab-sztn) IV • Tysabri (natalizumab) IV 	<p>Tysabri (natalizumab) is subject to review for site of service administration.</p> <p>Tyruko (natalizumab-sztn) and Tysabri (natalizumab) may be considered medically necessary for the treatment of</p>



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<p>relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, when the following conditions are met:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> The medication is not used concurrently with other MS disease modifying drugs <p>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.</p>
<p>CD20-directed cytolytic antibody</p> <ul style="list-style-type: none"> Briumvi (ublituximab-xiiy) IV 	<p>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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Briumvi (ublituximab-xiiy) is not used concurrently with other MS disease modifying drugs
<p>CD20-directed cytolytic antibody</p> <ul style="list-style-type: none"> Kesimpta (ofatumumab) SC 	<p>Kesimpta (ofatumumab) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p>



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<ul style="list-style-type: none"> Kesimpta (ofatumumab) is not used concurrently with other MS disease modifying drugs
CD20-directed cytolytic antibody <ul style="list-style-type: none"> Ocrevus (ocrelizumab) IV 	<p>Ocrevus (ocrelizumab) is subject to review for site of service administration.</p> <p>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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Ocrevus (ocrelizumab) is not used concurrently with other MS disease modifying drugs
Purine Antimetabolite <ul style="list-style-type: none"> Mavenclad (cladribine) Oral 	<p>Mavenclad (cladribine) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Mavenclad (cladribine) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> The individual has had an inadequate response to one or more disease modifying drugs indicated for the treatment of multiple sclerosis (any one of the following: B-interferon(s), dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer, monomethyl fumarate, natalizumab, ocrelizumab, ofatumumab, ozanimod, ponesimod, siponimod or teriflunomide)



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Mavenclad (cladribine) is limited to 2 treatment courses
<p>Sphingosine 1-Phosphate Receptor Modulator</p> <ul style="list-style-type: none"> Mayzent (siponimod) Oral 	<p>Mayzent (siponimod) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 7 <p>AND</p> <ul style="list-style-type: none"> Mayzent (siponimod) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> Documented test confirms the individual does NOT have CYP2C9*3/*3 genotype <p>AND</p> <ul style="list-style-type: none"> Dose is ≤ 2 mg per day <p>Note: Mayzent (siponimod) is contraindicated in individuals with CYP2C9*3/*3 genotype because of substantially elevated plasma levels of drug.</p>
<p>Sphingosine 1-Phosphate Receptor Modulator</p> <ul style="list-style-type: none"> Ponvory (ponesimod) oral 	<p>Ponvory (ponesimod) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Ponvory (ponesimod) is not used concurrently with other MS disease modifying drugs <p>AND</p>



Relapsing Multiple Sclerosis (RMS)	
Drug	Medical Necessity
	<ul style="list-style-type: none"> Dose is \leq 20 mg per day
Sphingosine 1-Phosphate Receptor Modulator <ul style="list-style-type: none"> Zeposia (ozanimod) oral 	<p>Zeposia (ozanimod) 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:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 6 <p>AND</p> <ul style="list-style-type: none"> Zeposia (ozanimod) is not used concurrently with other MS disease modifying drugs <p>AND</p> <ul style="list-style-type: none"> Dose is \leq 0.92 mg per day

Primary Progressive Multiple Sclerosis (PPMS)	
Drug	Medical Necessity
CD20-directed cytolytic antibody <ul style="list-style-type: none"> Ocrevus (ocrelizumab) IV 	<p>Ocrevus (ocrelizumab) is subject to review for site of service administration.</p> <p>Ocrevus (ocrelizumab) may be considered medically necessary for the treatment of primary progressive multiple sclerosis when the following conditions are met:</p> <ul style="list-style-type: none"> The individual must have an expanded disability status score (EDSS) of less than 7 <p>AND</p> <ul style="list-style-type: none"> Ocrevus (ocrelizumab) is not used concurrently with other MS disease modifying drugs

Drug	Investigational
As listed	All other uses of the medications listed in this policy are considered investigational.



Length of Approval	
Approval	Criteria
Initial authorization	Drugs listed in policy may be approved up to 12 months.
Re-authorization criteria	<p>Future re-authorization of drugs listed in policy, except Mavenclad (cladribine), 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.</p> <p>Future re-authorization of Mavenclad (cladribine) following the administration of two treatment courses is considered investigational.</p>

Documentation Requirements
<p>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:</p> <ul style="list-style-type: none"> Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	
J0202	Injection, alemtuzumab (Lemtrada), 1 mg
J1595	Injection, glatiramer acetate, 20 mg (used to report Glatopa and Copaxone)
J1826	Injection, interferon beta-1a (Avonex), 30 mcg
J1830	Injection interferon beta-1b (used to report Betaseron and Extavia), 0.25 mg
J2323	Injection, natalizumab (Tysabri), 1mg
J2329	Injection, ublituximab-xiyy (Briumvi), 1mg (new code effective 7/1/23)
J2350	Injection, ocrelizumab (Ocrevus), 1 mg



Code	Description
J3590	Unclassified biologics (used to report Kesimpta)
Q3027	Injection, interferon beta-1a (Avonex), 1 mcg for intramuscular use
Q3028	Injection, interferon beta-1a (Rebif), 1 mcg for subcutaneous use
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar (Tyruko), 1 mg (new code effective 4/1/2024)

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.

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. In 2000, the estimated prevalence was 191/100,000 Caucasians in the United States, 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.

Oral Agents for Multiple Sclerosis

Fingolimod is an oral modulator of sphingosine-1-phosphate receptor. After absorption, fingolimod is phosphorylated and fingolimod phosphate acts as agonist on the sphingosine-1-phosphate-1 receptors of the lymphocyte and thymocytes. This interaction results in the internalization of the receptor and thus without signaling the lymphocytes become sequestered within the lymph nodes. It is hypothesized that the resulting decrease in circulating lymphocytes then leads to fewer lymphocytes entering the CNS. Additionally, it is also hypothesized that when fingolimod crosses the BBB the resulting binding down modulates the S1P in neural cells and thus there is a reduction in the astrogliosis that can lead to neurodegeneration. Fingolimod has not been shown to inhibit the effector functions of T and B cells, humoral immunity, or virus-specific cytotoxic T cells.



The efficacy of fingolimod was demonstrated by two Phase III randomized placebo-controlled trials. Fingolimod was found to be significantly better than placebo at the strength of 0.5 mg at reducing the annualized relapse rate, MRI assessment measures, and disease progression measurements. The primary endpoint was reduction in annualized relapse rate over 24 months was 0.18 (0.15-0.22) for 0.5 mg fingolimod and 0.40 (0.34-0.47) for placebo with a p-value <0.001. This represents a 54% relative reduction in relapses as compared to placebo. Disease progression confirmed after 6 months had a probability of 12.5% for 0.5 mg fingolimod versus 19% for placebo.

Fingolimod was compared to IM interferon beta-1a in one clinical trial. Fingolimod proved superior in the primary endpoint of annualized relapse rate. The ARR for fingolimod 0.5 mg was 0.16 (0.12-0.21) versus 0.31 (0.22-0.41) for interferon beta-1a with a p-value <0.001. Additionally, fingolimod was superior in the secondary endpoint of T1 lesion amount. For fingolimod 0.5 mg the mean volume was 22.61 ± 111.59 versus 50.68 ± 198.16 for interferon beta-1a with a p-value of <0.001. However, fingolimod did not prove superior at prevention of disease progression as compared to interferon beta-1a.

Overall, fingolimod has a reasonable safety profile. There is a potential for bradycardia or AV block after administration of the first dose that may require monitoring. Additional concerns are potential increased susceptibility to infections, macular edema, and lymphopenia. The only deaths that occurred during the clinical trial were in the 1.25mg fingolimod arm and suffered a herpes zoster and herpes simplex encephalopathy infections, respectively.

Dimethyl fumarate, (Tecfidera) and diroximel fumarate (Vumerity) are oral agents indicated for the treatment of relapsing forms of MS (RMS). The exact mechanism whereby they exert therapeutic effects is unknown. However, dimethyl fumarate and its metabolite, monomethyl fumarate (MMF), activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which is involved in cellular response to oxidative stress and implicated in regulation of myelin maintenance in the central nervous system. In vitro, MMF has also been identified as a nicotinic acid receptor agonist.

Well designed and adequate evidence consistently supports the efficacy of dimethyl fumarate at approved dosing for reduction of relapse and improving neuroradiologic outcomes over 2 years in individuals with relapsing-remitting MS. Whether the agent is "disease modifying" or delays disease progression is unclear because of the conflicting results for 12-week confirmed disability progression from the two registrational Phase III trials.

After two years therapy in the placebo-controlled Phase III trials, the most common adverse events were mostly mild to moderate flushing and GI events (nausea, vomiting, and abdominal pain). Incidence of these events was highest in the first month of use and then generally



decreased thereafter. Discontinuation due to AEs was similar to that for placebo. Excepting for relapse of MS, SAEs were reported very infrequently. Mean lymphocyte counts decreased approximately 30% during the first year of treatment with dimethyl fumarate then levels plateaued. However, incidence of infections and serious infections were similar between individuals receiving the drug and those receiving placebo. Elevations in aminotransferase levels were also observed. In the Phase IIb study, transaminase elevations were considered dose related.

Aubagio (teriflunomide) is approved for use in individuals with relapsing forms of multiple sclerosis (MS). This medication acts as a pyrimidine synthesis inhibitor, functioning as an immunomodulatory agent that produces the anti-proliferative and anti-inflammatory effects. By decreasing the frequency and severity of MS symptoms flare-ups, Aubagio helps manage this condition. The efficacy and safety of Aubagio was determined in four randomized, double-blind clinical trials in individuals with relapsing form of multiple sclerosis.

Study 1 was a double-blind, placebo-controlled clinical trial where 1088 individuals with relapsing form of multiple sclerosis randomized to receive Aubagio 7 mg (n = 366), Aubagio 14 mg (n = 359), or placebo (n = 363). The main objective of the study was to assess the annualized relapse rate (ARR), which was achieved by both treatment groups and showed significant reductions in comparison to the placebo group. The Aubagio 7 mg group demonstrated ARR of 0.370 (p = 0.0002), the Aubagio 14 mg group demonstrated ARR of 0.369 (p = 0.0005), while the placebo group had an ARR of 0.539. Additionally, the individuals treated Aubagio 14 mg had a statistically significant reduction in the relative risk of disability progression at week 108, which was sustained for 12 weeks compared to placebo. At week 108, the percentage of disability progression was 21.7% (p = 0.084) for Aubagio 7 mg, 20.2% (p = 0.028) for Aubagio 14 mg and 27.3% for the placebo group. Moreover, individuals experienced a significant change in the total lesion volume from baseline to week 108, with a median change of 0.755 in Aubagio 7 mg group (p = 0.0317), 0.345 in Aubagio 14 mg group (p = 0.0003) and 1.127 in the placebo group. Individuals also experienced statistically significant reduction in the gadolinium (Gd)-enhancing lesions per T1 per scan, with mean number of Gd-enhancing T1-lesions per scan was 0.570 in Aubagio 7 mg, 0.261 in Aubagio 14 mg and 1.331 placebo group.

Study 2 was a double-blind, placebo-controlled clinical study where 1165 individuals with relapsing forms of multiple sclerosis received Aubagio 7 mg (n = 407), Aubagio 14 mg (n = 370), or placebo (n = 388). The primary efficacy endpoint was to assess annualized relapse rate (ARR), which was achieved by both treatment groups and showed significant reductions in comparison to the placebo group. The Aubagio 7 mg group demonstrated ARR of 0.389 (p = 0.0183), the Aubagio 14 mg group demonstrated ARR of 0.319 (p = 0.0001) and the placebo group had an ARR of 0.501. Additionally, the individuals treated Aubagio 14 mg had a statistically significant



reduction in the relative risk of disability progression at week 108, which was sustained for 12 weeks compared to placebo. At week 108, the percentage of disability progression was 21.2% ($p = 0.762$) in Aubagio 7 mg group, 15.8 % ($p = 0.044$) and 19.7% in the placebo group.

Study 3 was a double-blind, placebo-controlled clinical trial where 614 individuals with relapsing multiple sclerosis received Aubagio 7 mg ($n = 203$), Aubagio 14 mg ($n = 214$) or placebo ($n = 197$). The study analyzed the treatment and placebo arms based on the proportion of individuals who remained free of relapse. The results showed that the proportion of individuals who were free of relapse was higher in the treatment groups, with Aubagio 7 mg at 70.5% ($p < 0.05$) and Aubagio 14 mg at 72.2% ($p < 0.05$), compared to the placebo group at 61.7%.

Study 4 was a randomized, double-blind, placebo-controlled study where 179 individuals with multiple sclerosis were randomized to receive Aubagio 7 mg ($n = 62$), Aubagio 14 mg ($n = 57$) or placebo ($n = 61$). The primary efficacy endpoint was assessing the average number of unique active lesions/MRI scan during 36-week treatment, period which was achieved by both groups and showed significant reductions in compared to the placebo group. The mean number of unique active lesions per brain MRI scan during the 36-week treatment period was 1.06 ($p = 0.0234$) in Aubagio 7 mg group, 0.98 ($p = 0.0052$) in Aubagio 14 mg and 2.69 in the placebo group.

The most common adverse effects from the clinical trials were headache, elevated Alanine aminotransferase (ALT), diarrhea, alopecia, and nausea. The discontinuation in the study was most likely due to elevation in ALT.

Other Agents

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.



2018 Update

Annual Review: Literature review from 5/1/17 to 3/12/18. Zinbryta section removed due to withdrawal from market.

2019 Update

Reviewed prescribing information for all drugs listed in policy and no changes to indication and usage were identified. Added medical necessity criteria for Mavenclad (cladribine) and Mayzent (siponimod) for the treatment of relapsing forms of multiple sclerosis. Removed a separate Dosage and Quantity Limits table and inserted the applicable quantity limits from table into the medical necessity criteria.

2020 Update

Reviewed prescribing information for all drugs listed in policy and no changes to indication were identified. Added to Lemtrada (alemtuzumab) the following for two or more disease modifying drugs that can could be tried first: diroximel fumarate, monomethyl fumarate, and ozanimod. Added medical necessity criteria for Bafiertam (monomethyl fumarate), which is a metabolite of dimethyl fumarate, for the treatment of relapsing forms of multiple sclerosis with requirement the individual had tried Tecfidera (dimethyl fumarate) first.

2021 Update

Reviewed prescribing information for all drugs listed in policy. To reduce confusion regarding line of therapy removed reference to “first-line” from the interferon products, glatiramer products, dimethyl fumarate, Gilenya (fingolimod), Tysabri (natalizumab), Ocrevus (ocrelizumab), Mayzent (siponimod), Ponvory (ponesimod), and Zeposia (ozanimod) as these drugs are not restricted to first-line only therapy. Added to Lemtrada (alemtuzumab) the following for two or more disease modifying drugs for the treatment of multiple sclerosis that can could be tried first: ofatumumab and ponesimod. Added to Mavenclad (cladribine) the following for one or more disease modifying drugs for the treatment of multiple sclerosis that can could be tried first: diroximel fumarate, monomethyl fumarate, ofatumumab, ozanimod, and ponesimod.



2022 Update

Reviewed prescribing information for all drugs listed in policy and products available for the treatment of MS. Identified one new product and added Tascenso ODT (fingolimod) to policy with the identical coverage criteria as Gilenya (fingolimod). Tascenso ODT is an orally disintegrating tablet and is a new formulation of fingolimod that is placed on the tongue and allowed to dissolve before swallowing.

2023 Update

Reviewed prescribing information for all drugs listed in policy and products available for the treatment of MS. Added criteria for generic teriflunomide. Updated the criteria of Aubagio to require a trial and failure with generic teriflunomide first. Removed the requirement of trial and failure of Ocrevus step therapy before trying Kesimpta.

2024 Update

Reviewed prescribing information for all drugs listed in policy and products available for the treatment of MS. Added criteria for Tyruko (natalizumab-sztn). Removed step therapy requirement from Briumvi (ublituximab-xiiy) criteria.

References

1. Kappos L, Radue EW, O'Connor P, et al, for the FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010a;362(5):1-15.
2. Cohen JA, Barkhof F, Comi G, et al, for the TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010a;362(5)402-415.
3. Comi G, O'Connor, Montalban X, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. *Mult Scler*. 2010;16(2)197-207.
4. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med*. 2006;355:1124-1140.
5. O'Connor P, Comi G, Montalban X, et al. Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. *Neurology*. 2009;72:73-79.
6. Gilenya Prescribing Information. Novartis Pharmaceuticals, East Hanover, NJ. Revised September 2023.



7. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012;367(12):1087-1097.
8. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367(12):1098-1107.
9. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicenter randomized, double-blind, placebo-controlled phase IIb study. *Lancet* 2008;372:1463-1472.
10. Tecfidera (dimethyl fumarate) prescribing information. Biogen Idec Inc; Cambridge, MA. Revised December 2023.
11. Mayzent (siponimod) prescribing information. Novartis Pharmaceuticals Corporation; East Hanover, NJ. Revised August 2023.
12. Mavenclad (cladribine) prescribing information. EMD Serono, Inc; Rockland, MA. Revised December 2023.
13. Miller AE, Rhoades RW. Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs. *Curr Opin Neurology* 2012;25 Suppl:S4-10.
14. National Institute for Health and Clinical Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. Technology appraisal guidance 303. January 2014. Available at <https://www.nice.org.uk/guidance/ta303> Accessed December 25, 2023.
15. 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.
16. Aubagio (teriflunomide) prescribing information. Genzyme Corporation; Cambridge, MA. Revised December 2022.
17. Tyruko (natalizumab-sztn) prescribing information. Sandoz, Inc; Princeton, NJ. Revised August 2023.
18. Briumvi (ublituximab-xiyy) prescribing information. TG Therapeutics; Morrisville, NC. Revised December 2022.

History

Date	Comments
07/01/16	New policy, add to Prescription Drug section, approved June 14, 2016. This information was extracted from policy 5.01.550 and addresses medically necessary first and second line treatment options for multiple sclerosis.
11/01/16	Interim Review, changes approved October 11, 2016. Inclusion of a new agent daclizumab (Zinbryta), its criteria, and background. Also, included administration route for each of the agents listed in the "dosing" section.
01/01/17	Interim Review, changes approved December 13, 2016. Types of the first-line drugs to be tried before Zinbryta can be approved have been added for clarity.
01/27/17	Coding update. HCPCS code J0202 added to policy; it was inadvertently left off when the policy was extracted from 5.01.550 on 06/14/16.
05/01/17	Annual Review, changes approved April 11, 2017. Criteria for newly approved agent ocrelizumab have been added.
01/01/18	Coding update; added HCPCS code J2350 (new code effective 1/1/18)



Date	Comments
07/01/18	Annual Review, approved June 5, 2018. Literature review from 5/1/17 to 3/12/18. Zinbryta section removed due to withdrawal from market.
11/01/18	Interim Review, approved October 9, 2018. Added criteria for ocrelizumab as first line therapy for RRMS and for Copaxone 40mg stepped through generic equivalent.
08/01/19	Annual Review, approved July 9, 2019. Added criteria for Mavenclad (cladribine) and Mayzent (siponimod) for the treatment of relapsing forms of multiple sclerosis. Removed HCPCS codes J3490 and J3590.
12/01/19	Interim Review, approved November 12, 2019, effective March 5, 2020. Added site of service review for Ocrevus (ocrelizumab) (for dates of service on or after March 5, 2020). Effective December 1, 2019, updated coverage criteria for Mayzent (siponimod).
02/01/20	Interim Review, approved January 14, 2020. Added coverage criteria for Vumerity (diroximel fumarate) and updated coverage criteria for Tecfidera (dimethyl fumarate).
05/01/20	Interim Review, approved April 14, 2020. Added coverage criteria for Zeposia (ozanimod). Updated the indication for each drug to include reference to clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease as applicable based on prescribing information. Updated Ocrevus (ocrelizumab) criteria for primary progressive multiple sclerosis to include an EDSS of < 7 and to not be used concurrently with other MS disease modifying drugs.
07/01/20	Annual Review, approved June 9, 2020. Added coverage criteria for Bafiertam (monomethyl fumarate). Added to Lemtrada (alemtuzumab) the following for two or more disease modifying drugs that can could be tried first: diroximel fumarate, monomethyl fumarate, and ozanimod.
10/01/20	Interim Review, approved September 8, 2020. Added generic dimethyl fumarate to policy. Added site of service review for Tysabri (natalizumab) for dates of service on or after January 1, 2021. Added HCPCS code J1826.
01/01/21	Interim Review, approved December 8, 2020. Added coverage criteria for Kesimpta (ofatumumab) with requirement to use Ocrevus (ocrelizumab) first. Updated Tecfidera (dimethyl fumarate) criteria requiring trial with generic dimethyl fumarate first. Added HCPCS code J3590.
05/01/21	Interim Review, approved April 13, 2021. Added coverage criteria for Ponvory (ponesimod).
01/01/22	Annual Review, approved December 2, 2021. Removed reference to "first-line" from the interferon products, glatiramer products, dimethyl fumarate, Gilenya, Tysabri, Ocrevus, Mayzent, Ponvory, and Zeposia as these drugs are not restricted to first-line only therapy. Added to Lemtrada (alemtuzumab) the following for two or more disease modifying drugs for the treatment of multiple sclerosis that can could be tried first: ofatumumab and ponesimod. Added to Mavenclad (cladribine) the following for one or more disease modifying drugs for the treatment of multiple sclerosis that can could be tried first: diroximel fumarate, monomethyl fumarate, ofatumumab, ozanimod, and ponesimod.



Date	Comments
10/01/22	Annual Review, approved September 26, 2022. Added Tascenso ODT (fingolimod) to policy with identical coverage criteria as Gilenya (fingolimod). Added HCPCS codes Q3028. Changed the wording from "patient" to "individual" throughout the policy for standardization.
03/01/23	Interim Review, approved February 14, 2023. Added coverage for generic fingolimod. Updated criteria for Gilenya (fingolimod) and Tascenso ODT (fingolimod) requiring trial with generic fingolimod first. Added coverage for Briumvi (ublituximab-xiyy) for the treatment of relapsing forms of MS. Added Briumvi to HCPC code J3590.
06/01/23	Annual Review, approved May 9, 2023. Added criteria for generic teriflunomide. Updated the criteria for Aubagio to require documentation of inadequate response to or intolerance of generic teriflunomide first.
07/01/23	Coding update. New HCPCS code J2329 added to coding table.
10/01/23	Interim Review, approved September 12, 2023. Removed the requirement of trial and failure of Ocrevus step therapy before trying Kesimpta.
02/01/24	Annual Review, approved January 9, 2024. Added criteria for Tyruko (natalizumab-sztn). Added Tyruko to HCPC code J3590.
03/01/24	Interim Review, approved February 13, 2024. Removed step therapy requirement from Briumvi (ublituximab-xiyy) criteria.
04/01/24	Interim Review, approved March 12, 2024. Added new HCPCS code Q5134.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

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.



Discrimination is Against the Law

Premera Blue Cross (Premera) complies with applicable Federal and Washington state civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera provides free aids and services to people with disabilities to communicate effectively with us, such as qualified sign language interpreters and written information in other formats (large print, audio, accessible electronic formats, other formats). Premera provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, contact the Civil Rights Coordinator. If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation, you can file a grievance with: Civil Rights Coordinator — Complaints and Appeals, PO Box 91102, Seattle, WA 98111, Toll free: 855-332-4535, Fax: 425-918-5592, TTY: 711, Email AppealsDepartmentInquiries@Premera.com. You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Ave SW, Room 509F, HHH Building, Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at <https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status>, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at <https://fortress.wa.gov/oic/online-services/cc/pub/complaintinformation.aspx>.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

注意: 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY: 711)。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auunaga fesoasoan, e fai fua e leai se totagi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

ໂປດອຸລາ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ຄມມນມີພ້ອມໃຫ້ທ່ານ. ໂທ 800-722-1471 (TTY: 711).

注意事項: 日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 (TTY:711) まで、お電話にてご連絡ください。

PAKDAAR: Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

ប្រយ័ត្ន: បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតលុយ គឺអាចមានសំរាប់អ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

ማስታወሻ: የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም አርዳታ ድርጅቶች: በነጻ ሊያግኙዎት ተዘጋጅተዋል: ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው: 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-722-1471 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

ထိပ်စီး: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS: 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

توجہ: اگر بہ زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.