09-J4000-45

Original Effective Date: 04/01/23

Reviewed: 06/11/25

Revised: 07/15/25

Subject: Ublituximab-xiiy (Briumvi™)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by triad of inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. MS has been categorized into four types: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS. Although a cure for MS remains elusive, several treatment options slow the progression of the disease and reduce the frequency of relapses.

Ublituximab-xiiy is monoclonal antibody that is used to reduce the frequency of relapses and delay the accumulation of physical disability in patients with RRMS. It exerts its physiologic effects through binding to CD20 on the surface of B lymphocytes which results in antibody-dependent and complement-mediated cell lysis. Ublituximab is Food and Drug administration (FDA) approved for the treatment of relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

The efficacy of ublituximab for the treatment of relapsing multiple sclerosis was compared to teriflunomide in two randomized, double-blind trials. Subjects were required to have at least one relapse in the prior year, 2 relapses in the previous 2 years, or the presence of a T1 gadolinium-enhancing lesion in the previous year. The subjects were also required to have an Expanded disability status scale score from 0 to 5.5 at baseline. In both trials, ublituximab significantly reduced annualized MS relapse rates compared to teriflunomide (Study 1, 0.076 vs 0.188, relative reduction = 59%;Study 2,

0.091 vs 0.178, RR=49%). The proportion of patients with 12-week confirmed disability progression was also reduced in the subjects treated with ublituximab as compared to teriflunomide (5.2% vs 5.9%, risk reduction=16%). The mean number of T1 gadolinium- enhancing lesions per MRI and number of new or enlarging T2 lesions were significantly reduced for subjects treated with ublituximab as compared to teriflunomide. The most common adverse reactions that occurred were infusion reactions, upper and lower respiratory tract infections, herpes infections, extremity pain, insomnia, and fatigue.

POSITION STATEMENT:

Site of Care: If ublituximab-xiiy (Briumvi™) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

Initiation of ublituximab-xiiy (Briumvi™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member is diagnosed with **ONE** of the following forms of multiple sclerosis (MS):
    a. Relapsing remitting multiple sclerosis [RRMS]
    b. Active secondary progressive MS [SPMS]
    c. First clinical episode and member has MRI features consistent with MS
3. Ublituximab will not be used in combination with **ANY** of the following:
    a. Alemtuzumab (Lemtrada)
    b. Cladribine (Mavenclad)
    c. Dimethyl fumarate (Tecfidera)
    d. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Natalizumab (Tysabri)
    l. Ocrelizumab (Ocrevus)
    m. Ofatumumab (Kesimpta)
    n. Ozanimod (Zeposia)
    o. Peg-interferon beta-1a (Plegridy)
    p. Ponesimod (Ponvory ODT)
    q. Rituximab (Rituxan or biosimilars)

r. Siponimod (Mayzent)
s. Teriflunomide (Aubagio)

4. The member does not have an active Hepatitis B viral (HBV) infection
5. The initial dosage does not exceed 150 mg at week 0, followed by 450 mg at week 2 and then 450 mg every 24 weeks thereafter

Approval duration: 1 year

Continuation of ublituximab therapy **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has demonstrated a beneficial response to therapy for treatment of RRMS, active SPMS, or clinically isolated syndrome
2. Authorization/reauthorization for ublituximab has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member previously met all indication-specific initiation criteria
3. Ublituximab will not be in combination with **ANY** of the following:
    a. Alemtuzumab (Lemtrada)
    b. Cladribine (Mavenclad)
    c. Dimethyl fumarate (Tecfidera)
    d. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Natalizumab (Tysabri)
    l. Ocrelizumab (Ocrevus)
    m. Ofatumumab (Kesimpta)
    n. Ozanimod (Zeposia)
    o. Peg-interferon beta-1a (Plegridy)
    p. Ponesimod (Ponvory)
    q. Rituximab (Rituxan or biosimilars)
    r. Siponimod (Mayzent)
    s. Teriflunomide (Aubagio)
4. The dose does not exceed 450 mg every 24 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Administer under the close supervision of a healthcare professional with access to medical support to manage severe reactions, such as serious infusion reactions. See prescribing information for infusion rate.

- First infusion: 150 mg intravenous infusion over 4 hours
- Second infusion: 450 mg intravenous infusion over 1 hour administered two weeks after the first infusion
- Subsequent infusions: 450 mg intravenous infusion over 1 hour administered 24 weeks after the first infusion and ever 24 weeks thereafter
- Observe the patient for at least one hour after the completion of the first two infusions. Post-infusion monitoring of subsequent infusions is at physician discretion unless infusion reaction an/or hypersensitivity has been observed in association with the current or any prior infusion.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Active hepatitis B virus infection
- History of life-threatening infusion reaction to ublituximab

Precautions/Warnings

- Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue if a life-threatening or disabling infusion reaction occurs
- Infections: Serious, fatal, and life-threatening infections have occurred. Delay administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with and after discontinuation, until B-cell repletion
- Reduction in Immunoglobulins: Monitor the level of immunoglobulins at the beginning of treatment. Monitor during and after discontinuation of treatment, until B-cell repletion, and especially when recurrent serious infections are suspected. Consider discontinuing in patients

with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins

- Fetal risk: May cause fetal harm. Advise females of potential risk to a fetus and for at least 6 months after stopping.

BILLING/CODING INFORMATION:

HCPCS Coding

J2329	Injection, ublituximab-xiiy, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G35	Multiple sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the guideline creation. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

None

RELATED GUIDELINES:

Alemtuzumab (Lemtrada), 09-J2000-27
Cladribine (Mavenclad), 09-J3000-34
Dimethyl Fumarate (Tecfidera), Diroximel fumarate (Vumerity) and Monomethyl fumarate (Bafiertam), 09-J1000-96
Fingolimod (Gilenya™), 09-J1000-30
Multiple Sclerosis Self Injectable Therapy, 09-J1000-39
Natalizumab (Tysabri®) IV, 09-J0000-73

Ocrelizumab (Ocrevus), 09-J2000-78
Ofatumumab (Kesimpta), 09-J3000-84
Ozanimod (Zeposia), 09-J3000-70
Siponimod (Mayzent), 09-J3000-35
Teriflunomide (Aubagio), 09-J1000-82

OTHER:

None

REFERENCES:

1. Briumvi [prescribing information]. TG Therapeutics, Inc. Morrisville, NC. June 2024.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025 May 28]. Available from: http://www.clinicalpharmacology.com/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 May 28].
4. Lublin FD, Reingold, SC, Cohen JA et al. Defining the clinical course of multiple sclerosis. Neurology. 2014; 83: 278-286.
5. National Multiple Sclerosis Society. Available at http://www.nationalmssociety.org Accessed 01/27/23.
6. Rae-Grant A, Day GS, Marrie RA et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Jan 2023. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/898.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

04/01/23	New Medical Coverage Guideline.
07/01/23	Revision: Added HCPCS code J2329 and deleted code J3590.
11/15/23	Review and revision to guideline; consisting of including Glatopa in the position statement.
07/15/24	Review and revision to guideline; consisting of updating the position statement to remove step requirement.
07/15/25	Review and revision to guideline; consisting of updating the references.