Policy Number	**RX501.153**
Policy Effective Date	**03/15/2025**
Policy End Date	**12/31/2025**

Ublituximab-xiiy

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Ublituximab-xiiy (Briumvi®) **may be considered medically necessary** for the treatment of adult individuals with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease when meeting **ALL** of the following criteria:

- Hepatitis B virus (HBV) screening demonstrates that the individual is negative for active HBV, AND
- Absence of active infection, AND
- Not used in combination with another multiple sclerosis (MS) disease modifying agent, AND
- Not given concurrently with live vaccines. All immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiation of treatment.

Ublituximab-xiiy (Briumvi®) **is considered experimental, investigational and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Ublituximab-xiiy (Briumvi®) is an anti-CD20 monoclonal antibody designed to target a unique epitope on CD20 B-cells. Targeting CD20 using monoclonal antibodies is a therapeutic approach for the management of autoimmune disorders, such as relapsing forms of multiple sclerosis (RMS) to potentially alter the course of the disease by lessening the frequency of relapses and disease progression. (1) Overall, the precise mechanism by which ublituximab-xiiy exerts its therapeutic effects in multiple sclerosis is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ublituximab-xiiy results in cell lysis through mechanisms including antibody-dependent cellular cytolysis and complement-dependent cytolysis. (2)

Multiple Sclerosis (MS)
Multiple sclerosis is a disorder of the central nervous system (CNS) characterized by inflammation, demyelination and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or

progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease of only CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well. Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, and visual disturbances), resulting in a significant impact on quality of life for patients and their families. (3, 4)

Multiple sclerosis disease courses and their descriptions include the following (4):

- Clinically isolated syndrome (CIS) - is described as a first episode of inflammatory demyelination in the central nervous system that could become MS if dissemination in time and space are established.
- Relapsing-remitting MS (RRMS) – includes episodes of acute worsening of neurologic functioning (new symptoms or worsening of existing symptoms) with total or partial recovery and no apparent progression of disease. This can either be active (showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging T2 lesions on magnetic resonance imaging [MRI] over a specified time) or not active (showing no evidence of disease activity). RRMS can either be "worsening" demonstrated by increased disability confirmed over a specified time following a relapse or "stable" in which there is no evidence of increasing disability over a specified time following a relapse.
- Primary progressive MS (PPMS) – includes steadily worsening neurologic function (accumulation of disability) from the onset of symptoms without initial relapses of remission.
- Secondary progressive MS (SPMS) – described as following an initial relapsing-remitting course, the disease becomes more steadily progressive, with or without relapses. The term active indicates showing evidence of new relapses, new gadolinium-enhancing lesions and/or new enlarging T2 lesions on MRI over a specified time.

Regulatory Status

Ublituximab-xiiy (Briumvi®) is an intravenously infused medication approved by the U.S. Food and Drug Administration (FDA) on December 28, 2022, for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (SPMS) in adults. (2)

The following guidance for the use of ublituximab-xiiy (Briumvi®) is noted on the U.S. FDA label (2):

- Vaccination with live-attenuated or live vaccines is not recommended during treatment with ublituximab-xiiy (Briumvi) and after discontinuation, until B-cell repletion.
- Use of effective contraception is recommended in women of reproductive age and for a minimum of 6 months after stopping ublituximab-xiiy (Briumvi) due to a potential risk to fetus.

- Pregnancy testing is recommended for females of reproductive potential prior to each infusion of ublituximab-xiiy (Briumvi).
- The safety and efficacy of ublituximab-xiiy has not been established in the pediatric population.
- Ublituximab-xiiy is contraindicated in individuals with active Hepatitis B virus infection.
- Delay the administration of ublituximab-xiiy in individuals with an active infection.
- Administer Briumvi under close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions, such as serious infusion reactions.

Rationale

This policy was developed in March 2023 and is based on the U.S. Food and Drug Administration (FDA) labeled indications. The FDA approval of ublituximab-xiiy (Briumvi®) Is based on the following clinical studies. (2)

Ublituximab-xiiy (Briumvi®) demonstrated efficacy in 2 randomized, double-blind, double-dummy, parallel group, active comparator-controlled clinical trials of identical design, in patients with relapsing forms of multiple sclerosis (RMS) treated for 96 weeks (Study 1 NCT03277261; ULTIMATE 1 and Study 2 NCT03277248; ULTIMATE 2). Patients were randomized to receive either Briumvi, given as an IV infusion of 150 mg for the first infusion, 450 mg two weeks after the first infusion for the second infusion/second dose, and 450 mg every 24 weeks after the first infusion for subsequent doses (third infusion and beyond) with oral placebo administered daily; or teriflunomide, the active comparator, given orally as a 14 mg daily dose with IV placebo administered on the same schedule as Briumvi. Both studies enrolled patients who had experienced at least one relapse in the previous year, two relapses in the previous two years, or had the presence of a T1 gadolinium-enhancing lesion in the previous year. Patients were also required to have an Expanded Disability Status Scale (EDSS) score from 0 to 5.5 at baseline. Neurological evaluations were performed at baseline, every 12 weeks, and at the time of a suspected relapse. Brain magnetic resonance imaging (MRI) scans were performed at baseline and at Weeks 12, 24, 48, and 96.

The primary outcome of both ULTIMATE 1 and ULTIMATE 2 was the annualized relapse rate (ARR) over the treatment period. Additional outcome measures included: the total number of MRI T1 gadolinium-enhancing lesions by Week 96, the total number of new or enlarging MRI T2 hyperintense lesions by Week 96, and time to confirmed disability progression for at least 12 weeks. Disability progression was defined as an increase of greater than or equal to 1.0 point from the baseline EDSS score that was attributable to multiple sclerosis (MS) when the baseline score was 5.5 or less, and greater than or equal to 0.5 points when the baseline score was above 5.5. Confirmed disability progression was evaluated in a pooled analysis of Studies 1 and 2. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit 12 weeks after the initial documentation of neurological worsening.

In the ULTIMATE 1 study, 274 patients were randomized to Briumvi and 275 to teriflunomide. Of those randomized to Briumvi, 88% completed the 96-week treatment period; of those randomized to teriflunomide, 92% completed the 96-week treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age was 37 years, 97% were White, and 63% were female.

In the ULTIMATE 2 study, 272 patients were randomized to Briumvi and 273 to teriflunomide. Of those randomized to Briumvi, 93% completed the 96-week treatment period; of those randomized to teriflunomide, 88% completed the 96-week treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age was 35 years, 99% were White, and 65% were female.

In both the ULTIMATE 1 and ULTIMATE 2 study, Briumvi significantly lowered the ARR compared to teriflunomide. Briumvi statistically significantly reduced the number of T1 gadolinium-enhancing lesions and the number of new or enlarging T2 lesions in both studies compared to teriflunomide. There was no statistically significant difference in disability progression confirmed at 12 weeks between Briumvi-treated and teriflunomide-treated patients. Results for ULTIMATE 1 and ULTIMATE 2 are presented in Table 1.

Table 1: Key Clinical and MRI Endpoints in RMS Patients from Study 1 (ULTIMATE 1) and Study 2 (ULTIMATE 2)

	Study 1		**Study 2**	
Endpoints	**Briumvi 450 mg[7]**	**Teriflunomide 14 mg[7]**	**Briumvi 450 mg[7]**	**Teriflunomide 14 mg[7]**
Clinical Endpoints[1]				
Annualized Relapse Rate (Primary Endpoint)	0.076	0.188	0.091	0.178
Relative Reduction	59% (p<0.001)		49% (p = 0.002)	
Proportion of Patients with 12-week Confirmed Disability Progression[2,3] Risk Reduction (Pooled Analysis)[4]	5.2% Briumvi vs. 5.9% teriflunomide 16% (p = 0.510)			
MRI Endpoints[5]				
Mean Number of T1 Gd-enhancing Lesions Per MRI[6]	0.016	0.491	0.009	0.250
Relative Reduction	97% (p<0.001)		97% (p<0.001)	
Mean Number Of New Or Enlarging T2 Hyperintense Lesions Per MRI[6]	0.213	2.789	0.282	2.831
Relative Reduction	92% (p<0.001)		90% (p<0.001)	

gd-enhancing: gadolinium enhancing; MRI; magnetic resonance imaging; RMS: relapsing forms of multiple sclerosis
[1] Based on Modified Intent-to-Treat (mITT) Population, defined as all randomized patients who received at least 1 infusion of study medication and had 1 baseline and post-baseline efficacy assessment. Study 1: Briumvi (N=271), teriflunomide (N=274). Study 2: Briumvi (N=272), teriflunomide (N=272).
[2] Data prospectively pooled from Study 1 and Study 2: Briumvi (N=543), teriflunomide (N=546).
[3] Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or 0.5 point or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.
[4] Based on Hazard Ratio.
[5] Based on MRI-mITT population (mITT patients who have baseline and post-baseline MRI). Study 1: Briumvi (N=265), teriflunomide (N=270). Study 2: Briumvi (N=272), teriflunomide (N=267).
[6] At Week 96.
[7] Briumvi dosing by intravenous infusion: first dose of 150 mg, second dose 450 mg two weeks after the first; subsequent doses 450 mg every 24 weeks; teriflunomide dosing: 14 mg by mouth once daily.

In the exploratory analyses of the ULTIMATE 1 and ULTIMATE 2 study, a similar effect of Briumvi on the ARR was observed in subgroups defined by gender, prior non-steroid MS therapy, baseline disability (EDSS 3.5 or lower versus greater than 3.5), the number of relapses in the 2 years prior to study enrollment, and number of gadolinium-enhancing lesions at baseline.

Summary of Evidence
Based on two randomized, double-blind, double-dummy, parallel group, active comparator-controlled clinical trials of identical design (ULTIMATE 1 and ULTIMATE 2), ublituximab-xiiy (Briumvi®) may be considered medically necessary for the treatment of adults with relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease when meeting the criteria noted in the Coverage section above. Ublituximab-xiiy (Briumvi®) is considered experimental, investigational and/or unproven for all other indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J2329

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. TG Therapeutics. TG Therapeutics announces FDA approval of Briumvi™ (ublituximab-xiiy). December 28, 2022. Available at: <https://ir.tgtherapeutics.com> (accessed January 22, 2025).
2. FDA - Label Briumvi® (ublituximab-xiiy). Food and Drug Administration. October 2024. Available at: <https://www.accessdata.fda.gov> (accessed January 17, 2024).
3. National Institute of Neurological Disorders and Stroke (NINDS). Multiple Sclerosis: Hope through research. August 2020. Available at: <https://catalog.ninds.nih.gov> (accessed January 22, 2025).
4. The use of disease-modifying therapies in Multiple Sclerosis: Principles and current evidence. A consensus paper by the Multiple Sclerosis Coalition 2019: The Multiple Sclerosis Coalition. June 2019. Available at: <https://ms-coalition.org> (accessed January 22, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
03/15/2025	Document updated with literature review. Coverage unchanged. No new references, others updated.
03/15/2024	Reviewed. No changes.
08/15/2023	New medical document. Ublituximab-xiiy™ (Briumvi) may be considered medically necessary for the treatment of adult patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease when meeting all of the following criteria: Hepatitis B virus (HBV) screening demonstrates that the patient is negative for active HBV, AND absence of active infection, and not used in combination with another multiple sclerosis (MS) disease modifying agent, and not given concurrently with live vaccines. All immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiation of treatment. Ublituximab-xiiy™ (Briumvi) is considered experimental, investigational and/or unproven for all other indications.