NEW DRUG APPROVAL

Brand Name	Briumvi™
Generic Name	ublituximab-xiiy
Drug Manufacturer	TG Therapeutics, Inc

New Drug Approval

FDA Approval Date: December 28, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761238

Dispensing restriction: Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Axonal injury is also a prominent pathologic feature, especially in the later stages. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms.

Among central nervous system disorders, MS is the most frequent cause of permanent disability in young adults, aside from trauma. MS affects more females than males. A systematic review of 28 epidemiologic studies found that, from 1955 to 2000, the estimated female to male ratio of MS incidence increased from 1.4:1 to 2.3:1.

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease affecting approximately 400,000 people in the United States and 2.1 million people worldwide. MS affects quality of life, employment, social relationships, and patients' productivity. The total all-cause health care costs associated with MS including direct and indirect costs in the United States ranged from $8,528 to $52,244 per patient per year.

Efficacy

The efficacy of Briumvi™ was demonstrated in two randomized, double-blind, double-dummy, parallel group, active comparator-controlled clinical trials of identical design, in patients with RMS treated for 96 weeks [Study 1 (NCT03277261) and Study 2 (NCT03277248)]. 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 (Gd)-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 MRI scans were performed at baseline and at Weeks 12, 24, 48, and 96.

The primary outcome of both Study 1 and Study 2 was the annualized relapse rate (ARR) over the treatment period. Additional outcome measures included: the total number of MRI T1 Gdenhancing 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 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 Study 1, 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 Study 2, 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 Study 1 and Study 2, Briumvi™ significantly lowered the ARR compared to teriflunomide. Briumvi™ statistically significantly reduced the number of T1 Gd-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 Study 1 and Study 2 are presented in Table 1.

	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)	
	0.213	2.789	0.282	2.831

Mean number of new or enlarging T2 hyperintense lesions per MRI[6] Relative Reduction	92% (p<0.001)	90% (p<0.001)

[1] Based on Modified Intent-to-Treat (mITT) Population, defined as all randomized patients who received at least one infusion of study medication and had one 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 exploratory analyses of Study 1 and Study 2, 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 Gd-enhancing lesions at baseline.

Safety

ADVERSE EVENTS

The most common adverse reactions in RMS trials (incidence of at least 10%) were infusion reactions and upper respiratory tract infections. Table 2 summarizes the adverse reactions that occurred in RMS trials (Study 1 and Study 2). The most common cause of discontinuation in patients treated with Briumvi™ was infection (1.3%).

Table 2: The adverse reactions that occurred in RMS trials

Adverse Reactions	Briumvi™ 450 mg IV[a] (N=545) %	Teriflunomide 14 mg PO (N=548) %
Infusion reactions	48	12
Upper respiratory tract infections[b]	45	41
Lower respiratory tract infections[c]	9	7
Herpes virus-associated infections[d]	6	5
Pain in extremity	6	4
Insomnia	6	3
Fatigue	4	4

[a]The first dose of Briumvi™ was given as an intravenous (IV) infusion of 150 mg. The second dose was given as an IV infusion of 450 mg two weeks after the first infusion.

[b] Includes the following: nasopharyngitis, upper respiratory tract infection, respiratory tract infection, respiratory tract infection viral, pharyngitis, rhinitis, sinusitis, acute sinusitis, tonsillitis, laryngitis, chronic sinusitis, viral

pharyngitis, viral rhinitis, viral upper respiratory tract infection, chronic tonsillitis, pharyngitis streptococcal, sinusitis bacterial, and tonsillitis bacterial.

[c] Includes the following: bronchitis, pneumonia, tracheitis, tracheobronchitis, COVID-19 pneumonia, bronchitis bacterial, and pneumonia viral.

[d] Includes several related terms.

WARNINGS & PRECAUTIONS

- **Infusion Reactions**: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue Briumvi™ if a life-threatening or disabling infusion reaction occurs.
- **Infections**: Serious, including life-threatening and fatal infections, have occurred. Delay Briumvi™ 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 Briumvi™ and after discontinuation, until B-cell repletion.
- **Reduction in Immunoglobulins**: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with Briumvi™, until B-cell repletion, and especially when recurrent serious infections are suspected. Consider discontinuing Briumvi™ 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 reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for at least 6 months after stopping Briumvi™.

CONTRAINDICATIONS

- Active hepatitis B virus infection.
- History of life-threatening infusion reaction to Briumvi™.

Clinical Pharmacology

MECHANISMS OF ACTION

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.

Dose & Administration

ADULTS

- Hepatitis B virus screening and quantitative serum immunoglobulin screening are required before first dose.
- Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion.
- Administer Briumvi™ by intravenous infusion.
  - First Infusion: 150 mg intravenous infusion.
  - Second Infusion: 450 mg intravenous infusion two weeks after the first infusion.
  - Subsequent Infusions: 450 mg intravenous infusion 24 weeks after the first infusion and every 24 weeks thereafter.
- Must be diluted in 0.9% Sodium Chloride Injection, USP prior to administration.

- Monitor patients closely during and 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 and/or hypersensitivity has been observed.

Table 3: Recommended Dose, Infusion Rate, and Infusion Duration for MS

	Dose (mg) and Volume (mL) of Briumvi™	Volume (mL) of 0.9% Sodium Chloride Injection, USP[1]	Infusion Rate (mL/hour)	Duration[2]
First Infusion	150 mg (6 mL)	250	• Start at 10 mL per hour for the first 30 minutes. • Increase to 20 mL per hour for the next 30 minutes. • Increase to 35 mL per hour for the next hour. • Increase to 100 mL per hour for the remaining 2 hours.	4 hours
Second Infusion (2 weeks later)	450 mg (18 mL)	250 mL	• Start at 100 mL per hour for the first 30 minutes. • Increase to 400 mL per hour for the remaining 30 minutes.	1 hour
Subsequent Infusions (Once every 24 weeks)[3]	450 mg (18 mL)	250 mL	• Start at 100 mL per hour for the first 30 minutes. • Increase to 400 mL per hour for the remaining 30 minutes.	1 hour

[1] Withdraw and discard the required volume of 0.9% Sodium Chloride Injection, USP from the infusion bag following the preparation instructions,
[2] Infusion duration may take longer if the infusion is interrupted or slowed.
[3] Administer the first subsequent infusion 24 weeks after the first infusion.

PEDIATRICS

Safety and effectiveness in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustments needed.

HEPATIC IMPAIRMENT

No dosage adjustments needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 150 mg/6 mL (25 mg/mL) in a single-dose vial.