Ublituximab-xiiy (BRIUMVI) National Drug Monograph June 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Ublituximab-xiiy is an anti-CD20 antibody that targets the CD20 antigen on pre-B and mature B lymphocytes. This results in B-cell depletion via antibody-dependent and complement-dependent cytolysis.

Indication(s) Under Review in This Document

- Relapsing forms of multiple sclerosis (MS) including: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (active SPMS)

Dosage Form(s) Under Review

- Single dose vial for intravenous (IV) infusion: 150mg/6mL
- Recommended dosing: First infusion is 150mg, second infusion is 450mg two weeks after first infusion; maintenance dosing is 450mg every 24 weeks starting 24 weeks after the first infusion.

Clinical Evidence Summary

Efficacy Considerations

ULTIMATE I and II – Phase III trials

Two identically designed phase III trials were performed for ublituximab: ULTIMATE I and ULTIMATE II.[1] Both were 96-week double blind, double dummy randomized controlled trials of ublituximab labelled dosing vs. teriflunomide 14mg daily. Patients enrolled had a diagnosis of a form of relapsing MS, though the vast majority (98%) of both trials were comprised of patients with relapsing-remitting MS (RRMS). Active SPMS only comprised 2% or less of each trial. To be included in the studies, patients also had to have a baseline Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and at least one of the following: at least 2 relapses in the past 2 years, one relapse in the past year, or one gadolinium enhancing lesion in the past year. The average age of patients across the study groups ranged from 36.2 to 37 years old and over 60% of all participants were female. This is reflective of the typical

epidemiology of early RMS[2-3]. The studies were not racially diverse, with over 97% of participants across both studies being white.

The percent of patients who were DMT-naïve was similar between study groups in ULTIMATE I (59.8% and 59.1% of ublituximab and teriflunomide participants respectively), but in ULTIMATE II there were more people who were DMT-naïve in the teriflunomide group (57%) than the ublituximab group (50.7%). The most common (>10%) of the previous DMTs tried were interferons, glatiramer, and laquinimod (an S1P modulator not FDA approved, but approved for use for RRMS in Russia). In both studies, about half the participants had gadolinium enhancing lesions at baseline. Given the prior DMT distribution and the percent of patients with contrast enhancing lesions at baseline, standard of practice for most of these participants would be an intensification of DMT. Teriflunomide (the active comparator for this trial), glatiramer, and interferons are widely considered to be low-efficacy DMTs. Anti-CD20 antibodies already in use for MS (including rituximab, ocrelizumab, and ofatumumab) are all considered high efficacy DMTs. Switching a patient from glatiramer or an interferon to teriflunomide represents what would generally be considered a lateral switch in expected efficacy. S1P modulators are largely considered moderate to high efficacy DMTs, though laquinimod has mixed efficacy evidence. Thus, switching from laquinimod to teriflunomide likely represents a lateral or possibly de-escalation of DMT intensity. On the other hand, switching patients from an interferon, glatiramer, or laquinimod to ublituximab represents a likely intensification of DMT (based on prior efficacy knowledge of anti-CD20 antibodies). Thus, the two DMT options represented in this trial are not equal in intensification strategy and represent a bias to the ublituximab group for better efficacy outcomes.

The primary efficacy end point of both phase III trials was the annualized relapse rate (ARR) over 96 weeks. Suspected relapses were defined as a new or worsened neurologic symptom. All suspected relapses were entered as a case report from the treating neurologist and a blinded neurologist that performed an EDSS. That case report was then evaluated by an independent panel to determine if the relapse was a protocol-defined relapse. Of note, no imaging was required to assess relapses. The protocol had requirements that would rule out some possible instances of recrudescence (i.e. pseudo-relapse) as symptoms were required to be "attributable to multiple sclerosis only in the absence of fever or infection." However, there are many other etiologies of recrudescence, from overheating to other physical or emotional stress. Without imaging, recrudescence could be indistinguishable from a relapse in symptomology. This could have had an impact on both treatment arms. Secondary efficacy end points for both trials spanned additional imaging and disability related outcomes. These were tested in a hierarchal manner.

Ublituximab met the primary endpoint of a significantly lower ARR versus teriflunomide over 96 weeks (see Table 1) in both ULTIMATE trials. Secondary imaging-related endpoints including: average number of contrast enhancing lesions and new or enlarged non-enhancing lesions were also significant in favor of ublituximab. Percent of brain volume change and all disability-related secondary outcomes were not statistically significant.

Table 1: Efficacy results from clinical trials

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr>
<td>ULTIMATE I and II

2 Phase III trials

I: N=545
II: N= 544</td>
<td>96-week randomized 1:1, double-blind, double-dummy
<u>Key Inclusion Criteria:</u>
- 18-55 years old
- Relapsing form of MS
- 2 relapses in prior 2 years, 1 relapse in prior year, or one contrast enhancing lesion in prior year
- EDSS 0 – 5.5
- Neurologic stability for 30 days prior

<u>Key Exclusion Criteria:</u>
- Prior treatment with other anti-CD20 antibodies, alemtuzumab, natalizumab, teriflunomide, leflunomide, stem cell transplant
- Prior DMT within
o 24 months: cladribine
o 6 months: daclizumab, azathioprine, methotrexate, cyclophosphamide
o 90 days: fingolimod, experimental S1P modulators, IVIg, plasmapheresis
o 30 days: glatiramer, interferons, dimethyl fumarate, laquinimod, glucocorticoids
- 10 or more years disease duration with 2 or lower on EDSS</td>
<td>All results described as mean with 95% confidence interval except where noted.

<u>Primary:</u>
<table>
<tr><th></th><th colspan="3">ULTIMATE I</th><th colspan="3">ULTIMATE II</th></tr>
<tr><th></th><th>Ublituximab</th><th>Teriflunomide</th><th>p value</th><th>Ublituximab</th><th>Teriflunomide</th><th>p value</th></tr>
<tr><td>Adj ARR</td><td>0.08
(0.04 to 0.14)</td><td>0.19
(0.12 to 0.28)</td><td><0.001</td><td>0.09
(0.05 to 0.17)</td><td>0.18
(0.11 to 0.29)</td><td>0.002</td></tr>
</table>
<u>Secondary:</u>
<table>
<tr><th></th><th colspan="3">ULTIMATE I</th><th colspan="3">ULTIMATE II</th></tr>
<tr><th></th><th>Ublituximab</th><th>Teriflunomide</th><th>p value</th><th>Ublituximab</th><th>Teriflunomide</th><th>p value</th></tr>
<tr><td>Gd-enhancing lesions by week 96</td><td>0.02
(0.01 to 0.03)</td><td>0.49
(0.35 to 0.68)</td><td><0.001</td><td>0.01
(0 to 0.02)</td><td>0.25
(0.16 to 0.39)</td><td><0.001</td></tr>
<tr><td>New or enlarged non-enhancing lesions by week 96</td><td>0.21
(0.14 to 0.32)</td><td>2.79
(2.14 to 3.64)</td><td><0.001</td><td>0.28
(0.20 to 0.40)</td><td>2.83
(2.13 to 3.77)</td><td><0.001</td></tr>
<tr><td>% change in brain volume at week 96</td><td>-0.2
(-0.23 to -0.17)</td><td>-0.13
(-0.16 to -0.1)</td><td>-</td><td>-0.19
(-0.23 to -0.16)</td><td>-0.18
(-0.21 to -0.15)</td><td>-</td></tr>
<tr><td>Worsening disability at week 12 (%)</td><td colspan="6">Presented as pooled data
Ublituximab: 28 (5.2) Teriflunomide: 32 (5.9)</td></tr>
<tr><td>NEDA week 24 to 96 (%)</td><td>121
(44.6)</td><td>41
(15)</td><td>-</td><td>117
(43)</td><td>31
(11.4)</td><td>-</td></tr>
</table>
Adj ARR: Adjusted Annualized Relapse Rate
Gd: Gadolinium
NEDA: No evidence of disease activity</td>
</tr>
</table>

Safety Considerations[1,4]

- **Boxed warnings:** none
- **Contraindications:** active hepatitis B infection, history of life-threatening infusion reaction to ublituximab
- **Other warnings / precautions**:
    - **Infusion reactions –** Infusion reactions including fever, chills, headache, flu-like symptoms, tachycardia, nausea, erythema, or anaphylaxis have been reported. The

incidence of infusion reactions in ULTIMATE I and II was 48%. None of the reactions were fatal and less than 1% required hospitalization. Most reactions were seen with the first infusion. Prevention of infusion reactions can be done with pre-medication with a steroid, antihistamine, and acetaminophen. Careful observation and pausing or discontinuing infusion based on the severity of symptoms is also warranted. These are very similar reactions and management strategies to other anti-CD20 antibodies.

- **Infections –** Infection was the most common adverse reaction for ublituximab in ULTIMATE I and II with 56% incidence between the two studies. Of note, only about 5% of infections were determined to be serious infections. Infections include bacterial, fungal, and new or reactivated viral infections.
  - When possible, it is recommended to administer all immunizations for which a patient is due prior to starting ublituximab. For live vaccines, administer at least 4 weeks prior to initiation and for non-live vaccines, administer at least 2 weeks prior to initiation. Vaccination with live vaccines is not recommended while on ublituximab. Non-live vaccines can be administered while a patient is on ublituximab.
  - Decreased immunoglobulins were observed with ublituximab. Decreased IgM was reported in less than 1% of patients in the ULTIMATE studies. Declines in IgG and IgM below the lower limit of normal have been associated with higher infection rates. Consider monitoring immunoglobulins during treatment as clinically indicated.

- **Adverse reactions**
  - **Common** adverse events that occurred in at least 10% of the ublituximab participants in ULTIMATE I and II: upper respiratory tract infection, headache, fever, nausea, and infusion reaction.
  - **Serious Adverse Events (ADEs) / Deaths / Discontinuation:** Serious ADEs occurred in 10.8% of people on ublituximab in ULTIMATE I and II. Serious infection was the most common serious ADE and occurred in 5% of ULTIMATE I and II participants on ublituximab. Three deaths occurred in the ublituximab group: pneumonia, encephalitis after measles, and salpingitis after ectopic pregnancy.

Other Considerations[4]

- **Fetal Risk:** In mothers exposed to other anti-CD20 antibodies, transient B cell depletion and lymphocytopenia have been reported in the infant. A pregnancy test is recommended for anyone of childbearing potential prior to each infusion. People of childbearing potential should also be counselled to use effective contraception during treatment and at least 6 months after the last infusion.

Other Therapeutic Options

Alternative treatments for multiple sclerosis are listed in table 2 below:

Table 2 High Efficacy MS DMT Treatment Alternatives

Drug	Formulary status	Indication	Administration frequency and infusion duration	Median time to B cell repletion (anti-CD20 antibodies)
Ublituximab-xiiy	TBD	Relapsing forms of MS	Q6 month IV infusion Initial infusion: ~4 hours Subsequent infusion: ~1 hour	70 weeks
Rituximab and biosimilars	Rituximab-pvvr is Formulary, PA-F. All other rituximab formulations are nonformulary.	Relapsing forms of MS (off-label)	Q6 month IV infusion Initial infusion: ~7-8 hours Subsequent infusion: ~4-5 hours	52-64 weeks
Ocrelizumab	Formulary, PA-F	Relapsing forms of MS and Primary Progressive MS	Q6 month IV infusion Initial infusion: ~3-4 hours Subsequent infusion: ~2-4 hours depending on prior tolerance	72 weeks
Ofatumumab	Formulary, PA-F	Relapsing forms of MS	Monthly subQ injection	40 weeks
Natalizumab	Formulary, PA-F	Relapsing forms of MS	Monthly IV infusion 1 hour duration	
Alemtuzumab	Non-formulary	Relapsing forms of MS	Pulsed IV Infusion	
Cladribine	Non-formulary	Relapsing forms of MS	Pulsed oral medication	

Dosing and B-cell repletion data from each drug's prescribing information[5-7].

Projected Place in Therapy

- Ublituximab is an anti-CD20 antibody administered by IV infusion. It is FDA approved for relapsing forms of MS only. This includes: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and active secondary progressive multiple sclerosis (active SPMS).
- Two phase III studies demonstrated that patients on ublituximab had a significantly lower adjusted ARR, contrast enhancing lesion number, and new or enlarged non-contrast enhancing lesion burden change compared to teriflunomide at 96 weeks. Delay of disability progression was not statistically significant.
- The 2018 American Academy of Neurology (AAN) Practice Guideline for DMTs in adults with MS does identify ocrelizumab, another anti-CD20 antibody, as a high efficacy DMT[8]. Due to timing of its approval, ublituximab is not included in the 2018 AAN guidelines.
- The February 2023 Institute for Clinical and Economic Review (ICER) report on oral and monoclonal antibody treatments for relapsing forms of MS assessed comparative effectiveness of anti-CD20 antibodies. There was no statistically significant difference in ARR found between ublituximab, ocrelizumab, ofatumumab, and off-label rituximab[9].
- There is in vitro evidence that ublituximab has greater natural killer cell-mediated antibody-dependent cellular cytotoxicity than other anti-CD20 antibodies[10]. However, as the ICER report demonstrates, this does not necessarily indicate that there will be in vivo improved efficacy for multiple sclerosis.
- Ublituximab did not have a statistically significant difference in confirmed disability progression compared to teriflunomide. This is unlike ocrelizumab and ofatumumab that did have a significant difference. There are multiple factors that could have contributed to these differences; some of the most notable being dramatically smaller study population in ULTIMATE I and II, CDP definition differences between each drug's studies, and differences in baseline characteristics.
- Administration times of IV infused anti-CD20 antibodies vary (see table 2) with ublituximab having one of the shorter infusion times.
- Although there are many patient-specific considerations involved in choosing a DMT for relapsing forms of MS, anti-CD20 antibodies are a high efficacy DMT treatment option that may be an option for highly active MS, or for patients who have experienced therapeutic inefficacy from other DMTs.

References

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