Ofatumumab (Kesimpta)
National Drug Monograph
March 2022
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
- Ofatumumab is a CD20-directed cytolytic antibody. Ofatumumab binds to a small-loop epitope of CD20 close to the cell surface, inducing efficient complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. This allows for the expansion of an inflammatory response which results in demyelination leading to axonal damage, disruption of the blood–brain barrier, and demyelination within the brain and spinal cord.

Indication(s) Under Review in This Document
- Ofatumumab is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome (CIS), relapsing-remitting disease (RMS), and active secondary progressive disease (Active SPMS), in adults.

Dosage Form(s) Under Review

The recommended dosage of ofatumumab is:
Initial dosing of 20 mg by subcutaneous injection at Weeks 0, 1, and 2, followed by subsequent dosing of 20 mg by subcutaneous injection once monthly starting at Week 4.

Clinical Evidence Summary

Efficacy Considerations
- Ofatumumab has been studied
- Efficacy data are summarized in Table 1
Table 1: Efficacy results from pivotal clinical trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASCLEPIOS I</th>
<th></th>
<th>ASCLEPIOS II</th>
<th></th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>0.11 *</td>
<td>0.22</td>
<td>0.10*</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Confirmed Worsening of Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 3 months</td>
<td>10.9% **</td>
<td>15.0%</td>
<td>8.2%***</td>
<td>12.0%</td>
<td></td>
</tr>
<tr>
<td>Over 6 months</td>
<td>8.2%***</td>
<td>12.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New/Enlarging MRI T2 Lesions</td>
<td>0.72*</td>
<td>4.00</td>
<td>0.64*</td>
<td>4.15</td>
<td></td>
</tr>
<tr>
<td>MRI T1 Gadolinium Enhanced Lesions</td>
<td>0.01*</td>
<td>0.45</td>
<td>0.03*</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.001, **p=0.002, *** p=0.01

Ofatumumab received initial FDA approval in 2009 under the brand name Arzerra™ for treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.iii FDA approval of ofatumumab for MS was based on the results of 2 double-blind trials (ASCLEPIOS I and II) in a total of 1882 adults with relapsing MS.iv Patients were randomized to receive subcutaneous ofatumumab 20 mg every 4 weeks (following loading doses of 20 mg on days 1, 7, and 14) or oral teriflunomide 14 mg once daily for up to 30 months. Annualized relapse rate (ARR) was the primary efficacy endpoint. Secondary endpoints included the time to 3- and 6-month CDW on EDSS, time to 6-month confirmed disability improvement on EDSS, number of GdE lesions per MRI scan, number of new or enlarging T2 lesions on MRI per year, and rate of brain volume loss (BVL) from baseline. Post-hoc analyses were conducted to assess 3- and 6-month CDP, NEDA, and B-cell depletion. Ofatumumab was more effective than teriflunomide at reducing ARR in adults with relapsing forms of MS. In the intent-to-treat (ITT) populations in both trials (median duration of treatment was 85 weeks), the AAR was significantly lower in the ofatumumab groups than the teriflunomide groups (Table 1). Additionally, the relative risk of a relapse was reduced by ofatumumab in more than 50% in both trials. In the pooled analysis, ofatumumab significantly reduced the percentage of patients with confirmed disability worsening compared with teriflunomide at 3 months (10.9% ofatumumab vs. 15.0% teriflunomide; HR 0.66; P=0.002; 95% CI, 0.50 to 0.86); and 6 months (8.1% ofatumumab vs. 12.0% teriflunomide; HR 0.68; P=0.01; 95% CI, 0.50 to 0.92). No significant difference between groups was observed on confirmed disability improvement at 6 months (11.0% ofatumumab vs. 8.1% teriflunomide; HR 1.35; P=0.09; 95% CI, 0.95 to 1.92) Patients in the ofatumumab group were also less likely to experience worsening of disability or to accumulate more lesions compared to those taking teriflunomide. There were no significant differences between the two groups in regard to change in brain volume.iv,v,vi

A network meta-analysis was conducted to determine the relative effect of ofatumumab on annualized relapse rate and confirmed disability progression at 3 months and 6 months.vii Data from 34 RCTs were used to indirectly compare ofatumumab with other DMTs for the treatment of RMS. For the outcomes
of ARR, time to 3-month CDP and time to 6-month CDP, NMA results demonstrated ofatumumab demonstrated similar efficacy compared with other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab and ocrelizumab). For the outcomes of ARR, time to 3-month CDP and time to 6-month CDP, NMA results demonstrated ofatumumab was numerically superior, and in some cases statistically superior, to non-antibody DMTs.

### Safety Results from Clinical Trials:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Ofatumumab N=946</th>
<th>Teriflunomide N=936</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infections</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>Injection-Related Systemic Reactions</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Blood Immunoglobulin M Decrease</td>
<td>6%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- **Boxed warnings:** None
- **Contraindications:** Ofatumumab is contraindicated in patients with active Hepatitis B (HBV) infection.
- **Other warnings / precautions:**
  - Administer all live or live-attenuated vaccines at least 4 weeks prior and non-live vaccines at least 2 weeks prior to initiation of therapy. Screen for hepatitis B prior to initiation; do not administer to patients with active hepatitis B confirmed by hepatitis B surface antigen (HBsAg) and anti-hepatitis B virus (HBV) tests. For patients with past HBV infections who are negative for HBsAg and positive for hepatitis B core antibody [HBCab+] or are chronic carriers of HBV [HBsAg+], consult liver specialists before starting and during treatment.
  - In high-risk populations or in countries with high tuberculosis burden, screen for latent infections (eg, hepatitis, tuberculosis) prior to initiating therapy. For patients who screen positive for latent infections, consult infectious disease or other specialists (eg, liver specialists) regarding treatment options before initiating therapy.

- **Adverse reactions**
  - In the phase III trials, adverse events (AEs) were reported in 83.6% of ofatumumab recipients (791 of 946) and 84.2% of teriflunomide recipients (788 of 936).
  - Upper respiratory tract infection, systemic and local injection-related reactions, headache, urinary tract infection, back pain, and decreased blood immunoglobulin M levels occurred more frequently with ofatumumab than with teriflunomide in the ASCLEPIOS trials. Systemic injection-related reactions were most common within 24 hours after the first injection.
  - Fatal PML has occurred with use of IV ofatumumab for treatment of CLL; the doses used for CLL are higher than those used for MS. Use of other anti-CD20 antibodies in patients with hepatitis B virus (HBV) infection has resulted in HBV reactivation, hepatic failure, and death; ofatumumab is contraindicated for use in patients with active HBV infection.
During the clinical trials, 1 death occurred due to fatal aortic hemorrhage in a patient treated with teriflunomide.

**Other Considerations**

No adequate data on the use of ofatumumab in pregnant or lactating women are available. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants whose mothers received anti-CD20 antibodies during pregnancy. Women of childbearing potential should use effective contraception while receiving ofatumumab and for 6 months after stopping the drug. Live vaccines should not be administered to neonates and infants who were exposed to ofatumumab in utero until B-cell repletion occurs.

**Other Therapeutic Options**

Alternative monoclonal antibody treatments for RMS are listed in table 3 below.

**Table 3  Treatment Alternatives**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulary status</th>
<th>Clinical Guidance</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab</td>
<td>NF, CFU</td>
<td>FDA approved for treatment of relapsing forms of multiple sclerosis, to include relapsing remitting disease and active secondary progressive disease, in adults. Because of safety profile, the FDA recommends that this medication generally, be reserved for people who have had an inadequate response to two or more MS therapies. REMS program</td>
<td>May cause serious, sometimes fatal, autoimmunity, infusion reactions, stroke and malignancies. Black box warning: risk for autoimmunity, (immune thrombocytopenia, Antiglomerular basement membrane disease) life threatening infusion reactions, malignancy, (melanoma, thyroid cancer, lymphoproliferative diseases)</td>
</tr>
<tr>
<td>natalizumab</td>
<td>F, PA</td>
<td>FDA approved as monotherapy for the treatment of relapsing forms of multiple sclerosis, which include clinically isolated syndrome, relapsing remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses). REMS program</td>
<td>PML risk, Antibody formation, Melanoma, Hepatic injury, Herpes encephalitis meningitis, immunosuppression, JCV positivity, prolonged use longer than 2 years</td>
</tr>
<tr>
<td>ocrelizumab</td>
<td>F, PA</td>
<td>FDA approved for the treatment of relapsing forms of multiple sclerosis in adults, which include clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses). Ocrelizumab is also approved by the FDA to treat primary progressive MS in adults.</td>
<td>Infections, including respiratory tract infections, herpes and potentially PML, -Hepatitis B reactivation, -Possible increased immunosuppressive effect if immunosuppressant used prior to or after ocrelizumab</td>
</tr>
</tbody>
</table>
Ofatumumab is a subcutaneously administered anti-CD20 antibody FDA-approved for treatment of adults with relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive MS.

Ofatumumab significantly improved the adjusted annualized relapse rate compared with teriflunomide in ASCLEPIOS I (0.11 vs. 0.22, respectively; difference -0.11; 95% confidence interval [CI], -0.16 to -0.06; P<0.001) and in ASCLEPIOS II (0.10 vs. 0.25, respectively; difference -0.15; 95% CI, -0.20 to -0.09; P<0.001).

In pooled analysis of both trials, the percentage of patients with confirmed worsening disability was significantly reduced with ofatumumab compared with teriflunomide at 3 months based on moderate-quality evidence [10.9% ofatumumab vs. 15.0% teriflunomide; hazard ratio (HR) 0.66; P=0.002; number need to treat (NNT) 25]; and at 6 months (8.1% vs. 12.0%; HR 0.68; P=0.01; NNT 26).

Adverse events that occurred in at least 10% of patients treated with ofatumumab included injection-related reactions, nasopharyngitis, headache, injection site reaction, upper respiratory tract infection, and urinary tract infection; events that occurred in at least 10% of those treated with teriflunomide included nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache, and diarrhea.

Ofatumumab is contraindicated in patients with active hepatitis B virus infection.

Ofatumumab may improve adherence through convenient and infrequent self-administration compared to the infusible agents in MS.

In a network meta-analysis demonstrated that ofatumumab was as effective as other highly efficacious monoclonal antibody DMTs (i.e., alemtuzumab, natalizumab and ocrelizumab for the outcomes of ARR and CDP/worsening at 3 and 6 months.

Reference

i Ofatumumab (Kesimpta) Product Labeling. Novartis Pharmaceuticals Corporation. 2021
ii Ofatumumab (Kesimpta) Formulary Submission Dossier. Novartis Pharmaceuticals Corporation. 2021
iii ARZERRA (ofatumumab) Intravenous Injection Prescribing Information Research Triangle Park, NC; GlaxoSmith Kline 10/2009
vii Samjoo IA, Worthington E, Drudge C, Zhao M, et al. Comparison of ofatumumab and other

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