Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Ofatumumab (Arzerra®)	MP-RX-FP-132-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Ofatumumab (Arzerra®),* a CD20-directed cytolytic monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of certain patients with chronic lymphocytic leukemia (CLL).

Background Information

Ofatumumab is also available as Kesimpta, a subcutaneous injection approved by the FDA for relapsing multiple sclerosis. This document only addresses the use of ofatumumab for CLL.

Arzerra is only available through the manufacturer's (Novartis Pharmaceutical Corporation) oncology patient access program. It is a human monoclonal antibody that specifically binds to both the small and large extracellular loops of the CD20 molecule. CD20 is expressed on normal B lymphocytes and B-cell chronic lymphocytic leukemia (CLL). Ofatumumab's Fab domain binds to CD20, and its Fc domain mediates immune effector functions, leading to B-cell lysis in vitro. Mechanisms of cell lysis may include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

The FDA approved indications for Arzerra in CLL include as a first line agent in combination with chlorambucil for treatment of previously untreated patients for whom fludarabine-based therapy is considered inappropriate. It is also approved in combination with fludarabine and cyclophosphamide for patients with relapsed disease, or as a single agent for those refractory to fludarabine and alemtuzumab. Arzerra is also approved as extended therapy. For extended therapy, Arzerra was studied as a maintenance treatment for 24 months in patients who were in complete or partial response after at least 2 lines of prior therapy. Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are managed in much the same way.

Ofatumumab comes with specific warnings and precautions outlined in the prescribing information. These include the potential for infusion reactions during administration, the risk of hepatitis B virus reactivation and infection, as well as the possibility of progressive multifocal leukoencephalopathy. Tumor lysis syndrome, cytopenias, and considerations regarding immunizations are also highlighted as important cautions. Healthcare providers prescribing ofatumumab should be vigilant about these potential risks and take necessary precautions to mitigate adverse effects in patients receiving this medication.

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Definitions and Measures

- Complete Response (CR): The disappearance of all signs of cancer as a result of treatment; also called complete remission; does not indicate the cancer has been cured.
- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Maintenance therapy: Designed to maintain a condition to prevent a relapse. One line of therapy: Single line of therapy.
- One line of therapy: Single line of therapy.
- Partial response (PR): A decrease in the size of a tumor, or in the amount of cancer in the body, resulting from treatment; also called partial remission.
- Progressive Disease (PD): Cancer that is growing, spreading, or getting worse. Refractory Disease: Illness or disease that does not respond to treatment.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Arzerra (ofatumumab) has a black box warning for hepatitis B reactivation which, in some cases, results in fulminant hepatitis, hepatic failure, and death. Arzerra also has a black box warning for progressive multifocal leukoencephalopathy which can occur in patients receiving CD20-directed antibodies, including Arzerra.

Approved Indications

A. Treatment of chronic lymphocytic leukemia (CLL):
   - In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.
   - In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL.
   - For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.
   - For the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

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Other Uses

i. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Arzerra. These include the use in CLL/SLL as a first line therapy in combination with bendamustine; however, supportive text indicates this recommendation comes from one non-comparative phase 2 study (Flinn 2016). In 2023, NCCN no longer recommend these addtional uses in B-cell Lymphomas and CLL/SLL.

ii. NCCN also recommends the use of Arzerra in Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma in those intolerant to rituximab, supported by an open-label, single arm phase 2 study.

iii. NCCN also lists a 2A recommendation for Arzerra as a substitute for rituximab in patients experiencing rare mucocutaneous reactions; however, it is unclear if the use of an alternative anti-CD20 antibody poses the same risk of recurrence (B-cell Lymphomas Guideline).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9302	Injection, ofatumumab, 10 mg [Arzerra]

ICD-10	Description
C83.00-C83.09	Small cell B-cell lymphoma [specified as small lymphocytic lymphoma]
C88.0	Waldenstrom macroglobulinemia
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Clinical Criteria

Ofatumumab (Arzerra®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (Label; NCCN 2A); **AND**

ii. Individual is using for one of the following:
   - A. As first line therapy in combination with chlorambucil; **OR**
   - B. Treatment of relapsed or refractory CLL/SLL, as a single agent and only in one line of therapy, *or* in combination with fludarabine and cyclophosphamide; **OR**
   - C. As maintenance treatment for up to 24 months when the following criteria are met:
     1. Treatment is following at least 2 lines of therapy for relapsed or progressive disease; **AND**
     2. A complete or partial response has been achieved;

OR

iii. Individual has a diagnosis of Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (NCCN 2A); **AND**
   - A. Individual is rituximab-intolerant; **AND**
   - B. Individual is using as a single agent or in combination; **AND**
   - C. Individual is using when previously treated disease did not respond to primary therapy or for progressive or relapsed disease.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Ofatumumab (Arzerra®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen and the maximum duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

ii. Maximum duration of therapy:
A. For previously untreated CLL: Up to 12 cycles
B. For relapsed CLL: Up to 6 cycles
C. As extended treatment in CLL: Up to 2 years
D. For refractory CLL: Up to 12 dosis

C. Authorization Duration

i. Initial Approval Duration: Per cycle for up to 3 months
ii. Reauthorization Approval Duration: Per cycle for up to 3 months (until the maximum duration of treatment is reached)

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Treatment of multiple sclerosis;

OR

ii. All other indications not included above.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

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Drug	Recommended Dosing Schedule
Previously untreated CLL	The recommended dosage and schedule in combination with chlorambucil is: • 300 mg on Day 1, followed 1 week later by 1,000 mg on Day 8 (Cycle 1), followed by • 1,000 mg on Day 1 of subsequent 28-day cycles **for a minimum of 3 cycles until best response or a maximum of 12 cycles**.
Relapsed CLL	The recommended dosage and schedule in combination with fludarabine and cyclophosphamide is: • 300 mg on Day 1, followed 1 week later by 1,000 mg on Day 8 (Cycle 1), followed by • 1,000 mg on Day 1 of subsequent 28-day cycles **for a maximum of 6 cycles**.
Extended treatment in CLL	The recommended dosage and schedule as single-agent extended treatment in CLL is: • 300 mg on Day 1, followed by • 1,000 mg 1 week later on Day 8, followed by • 1,000 mg 7 weeks later and every 8 weeks thereafter **for up to a maximum of 2 years.**
Refractory CLL	The recommended dosage and schedule **is 12 doses** administered as follows: • 300 mg initial dose on Day 1, followed 1 week later by • 2,000 mg weekly for 7 doses (Infusions 2 through 8), followed 4 weeks later by • 2,000 mg every 4 weeks for 4 doses (Infusions 9 through 12).
Exceptions and additional information	
- Premedications include intravenous corticosteroid (prednisolone or equivalent), oral acetaminophen, and oral or intravenous antihistamine.	

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: December 29, 2022.

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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamusting combination in patients with untreated or relapsed CLL. Am J Hematol 2016; 91: 900-906.
5. Furman RR, eradat H, Switzky JC, et al. A phase 2 trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia [abstract]. Blood 2010; 116: Abstract 1795.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
7. NCCN Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on December 29, 2022.
    a. Waldenstròm Macroglobulinemia/Lymphoplasmacytic Lympoma. V1.2023. Revised July 6, 2022.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 12/10/2024	Remove Waldenström's criteria from may not be approved criteria. Add NCCN 2A recommendation for use in Waldenstrom Macrogloblinemia/ Lymphoplasmocytic Lymphoma. Remove NCCN reference for CLL/SLL use, no longer discussed in the NCCN guidelines for CLL/SLL. Coding Reviewed: Added ICD-10-CM C88.0.	3/20/2025	4/2/2025
Policy Inception 1/16/2024	New Medical Policy creation	4/18/2024	6/28/2024