Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Obinutuzumab (Gazyva®)	MP-RX-FP-33-23	☒ 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 Obinutuzumab (Gazyva®), CD20-directed cytolytic antibody, approved by the Food and Drug Administration (FDA) for the treatment of certain patients with Chronic Lymphocytic Leukemia (CML), Bulky, and Follicular Lymphoma

Background Information

Gazyva is FDA approved in combination with chlorambucil for previously untreated CLL. CLL and SLL are different manifestations of the same disease and are managed in much the same way. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Gazyva. NCCN recommends it to be used as first line treatment for patients without del (17p) mutation, in combination with either chlorambucil or bendamustine. NCCN also recommends Gazyva first line as a single agent for those with del (17p) mutation (2A recommendation) and for frail patients without del (17p) mutation (2B recommendation). It is also recommended as a single agent in patients without del (17p) mutation in relapsed or refractory disease. Venetoclax was recently granted FDA approval for treatment of CLL/SLL based on a study of Gazyva in combination with venetoclax as first line therapy in those with CLL/SLL with or without del (17p) mutation. Similarly, acalabrutinib (Calquence) and Ibrutinib (Imbruvica) have FDA approval in combination with Gazyva for first line therapy of CLL/SLL.

Gazyva is also FDA approved to treat follicular lymphoma (FL), a type of B-cell lymphoma. It is indicated in combination with bendamustine followed by monotherapy for up to 2 years for treatment of FL which has relapsed after or is refractory to a rituximab- containing regimen. It is also approved in combination with bendamustine, CHOP regimen, or CVP regimen followed by monotherapy for up to 2 years for previously untreated FL.

Definitions and Measures

- CHOP regimen: Cyclophosphamide, doxorubicin, vincristine, and prednisone CVP regimen: Cyclophosphamide, vincristine, and prednisone
- Del (17p) mutation: A cytogenetic abnormality which reflects the loss of the TP53 gene and is frequently associated with mutations in the remaining TP53 allele, and is associated with short treatment-free interval, short median survival, and poor response to chemotherapy

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- Follicular Lymphoma: A type of B-cell non-Hodgkin lymphoma, a cancer of the immune system that is usually indolent (slow-growing). The tumor cells grow as groups to form nodules. There are several subtypes of follicular lymphoma.
- 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.
- Non-Hodgkin Lymphoma (NHL): A group of malignant solid tumors or lymphoid tissues. One line of therapy: Single line of therapy.
- 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.

Approved Indications

Gazyva's FDA indications include:

- Patients with previously untreated chronic lymphocytic leukemia: In combination with chlorambucil
- Patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen: in combination with bendamustine followed by Gazyva monotherapy.
- Adult patients with previously untreated stage II bulky, III or IV follicular lymphoma achieving at least a partial remission: in combination with chemotherapy followed by Gazyva monotherapy

Other Uses

NCCN guideline for B-cell Lymphomas include 2A recommendations for the use of Gazyva for multiple types of refractory non-Hodgkin lymphomas (NHL) (gastric MALT lymphoma, nodal marginal zone lymphoma (MZL), non-gastric MALT lymphoma, and splenic MZL). One open label randomized phase 2 trial compared the efficacy and safety of rituximab to Gazyva as both induction and maintenance therapy in indolent NHLs (Sehn 2015). This trial recruited few patients with non-follicular lymphoma; and there was no difference in PFS between groups. The rationale for the 2A recommendation references the GADOLIN study which included patients with MZL. GADOLIN was an open label, multicenter, randomized phase 3 study to evaluate Gazyva plus bendamustine versus bendamustine alone in patients with indolent NHLs. Analysis of the subset of patients with FL, in part, informed FDA approval for FL. The overall study recruited few patients with MZL (47 total) and only results of the entire intent-to-treat population were reported (Cheson 2018). NCCN recommends Gazyva as a single agent and in combination with lenalidomide for second line or subsequent therapy in follicular lymphoma, but no literature is cited to support these uses. NCCN also lists a 2A recommendation for Gazyva 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.

Gazyva has a black box warning for hepatitis B (HBV) reactivation which, in some cases, results in fulminant hepatitis, hepatic failure, and death. Gazyva and concomitant medications should be discontinued in the event of HBV reactivation. Gazyva also has a black box warning for progressive multifocal leukoencephalopathy (PML), including fatal PML, which can occur in patients receiving Gazyva.

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
J9301	Injection, obinutuzumab, 10 mg [Gazyva]

ICD-10	Description
C82.00-C82.99	Follicular lymphoma
C83.00-C83.09	Small cell B-cell lymphoma
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
C91.40-C91.42	Hairy cell leukemia

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.

Obinutuzumab (Gazyva®)

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; **AND**
ii. Individual is using for one of the following:

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A. In combination with bendamustine for first-line treatment in individuals without del (17p)/TP53 mutation (NCCN 2A);

OR

B. In combination with chlorambucil for first-line treatment in individuals without del(17p)/TP53 mutation who have significant comorbidity or age ≥65 (Label, NCCN 2A); **OR**

C. In combination with ibrutinib for first-line treatment in individuals without del(17p)/TP53 mutation who have significant comorbidity or age ≥65 (Ibrutinib label, NCCN 2B); **OR**

D. In combination with venetoclax for first-line treatment in individuals with or without del (17p)/TP53 mutation (NCCN 2A); **OR**

E. In combination with acalabrutinib for first-line treatment in individuals with or without del (17p)/TP53 mutation; **OR**

F. As a single agent for first-line treatment in individuals who are frail *or* with del (17p)/TP53 mutation (NCCN 2A); **OR**

G. As a single agent for treatment of relapsed/refractory disease without del (17p)/TP53 mutation (NCCN 2A);

OR

iii. Individual has a diagnosis of follicular lymphoma; **AND**

iv. Individual is using in combination with one of the following regimens *and continue* as monotherapy, for up to 24 months or until disease progression, following the listed combination therapy regimens:

A. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen); **OR**

B. Cyclophosphamide, vincristine, and prednisone (CVP regimen); **OR**

C. Bendamustine; **OR**

D. Zanubrutinib;

OR

v. Individual has a diagnosis of hairy cell leukemia (NCCN 2A); **AND**

vi. Individual is using as initial therapy who are unable to tolerate purine analogs; **AND**

vii. Individual is using in combination with vemurafenib.

OR

viii. Individual has a diagnosis of Mantle Cell Lymphoma; **AND**

ix. Individual has classical or indolent TP53 mutated disease; **AND**

x. Individual is using in combination with venetoclax; **AND**

xi. Clinical trials are not available or appropriate for treatment.

OR

xii. Individual is using as monotherapy for up to 24 months or until disease progression; **AND**

xiii. Individual has one of the following diagnoses:

A. Follicular Lymphoma; **OR**

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B. Nodal or splenic marginal zone lymphoma; **OR**
C. Non-cutaneous extranodal marginal zone lymphoma;

OR

xiv. Individual has a diagnosis of relapsed, refractory, or progressive noncutaneous extranodal marginal zone lymphoma (NCCN 2A); **AND**
xv. Individual is using in combination with one of the following regimens:
   A. Bendamustine; **OR**
   B. Lenalidomide;

OR

xvi. Individual has a diagnosis of relapsed, refractory, or progressive nodal or splenic marginal zone lymphoma (NCCN 2A); **AND**
xvii. Individual is using in combination with one of the following regimens:
   A. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen); **OR**
   B. Cyclophosphamide, vincristine, and prednisone (CVP regimen); **OR**
   C. Bendamustine; **OR**
   D. Lenalidomide

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Obinutuzumab (Gazyva®) 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 an 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. Chronic Lymphocytic Leukemia: Up to 6 cycles
   B. Follicular Lymphoma:
      1. Initial treatment is 6-8 cycles.
      2. MMM considers additional maintenance treatment clinically appropriate in patients who achieve stable disease, complete response, or partial response to the initial 6-8 cycles (evidence should be submitted for reauthorization). Maximum duration of treatment is 2 years.

C. Authorization Duration

i. Initial Approval Duration: Per cycle
ii. Reauthorization Approval Duration: As requested (up to 6 months)

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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 diffuse large B-cell lymphoma; **OR**

ii. May not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. 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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Use	Cycles Duration	Recommended Dosing Schedule	Total Duration of Therapy
Chronic Lymphocytic Leukemia	28 days	Cycle 1 (loading doses): • Day 1: 100 mg • Day 2: 900 mg • Day 8: 1,000 mg • Day 15: 1,000 mg Cycles 2-6: Gazyva 1,000 mg on Day 1	6 Cycles
Follicular Lymphoma			
Relapsed or Refractory FL	Cycles 1-6: 28 days	• Cycle 1 (loading doses): 1,000 mg administered on Days 1, 8, and 15 • Cycles 2-6: 1,000 mg on Day 1	Up to 2 years (in patients who achieve stable disease, complete response, or partial response to the initial 6 cycles)
	Maintenance: Every 2 months (after the initial 6-8 cycles)	1,000 mg i.v. every two months as monotherapy	
Previously untreated FL	*Option a*: <u>28-days cycle</u> Six 28-days cycles in combination with bendamustine	• Cycle 1 (loading doses): Gazyva 1,000 mg i.v. on Days 1, 8, and 15 (with bendamustine) • Cycles 2-6: Gazyva 1,000 mg i.v. on Day 1 (with bendamustine)	Up to 2 years (in patients who achieve stable disease, complete response, or partial response to the initial 6-8 cycles)
	Option b: <u>21-days cycles</u> Six 21-day cycles in combination with CHOP, followed by 2 additional 21-day cycles of Gaziva alone.	• Cycle 1 (loading doses): 1,000 mg i.v. on Days 1, 8, and 15 (with CHOP) • Cycles 2-6: Gazyva 1,000 mg i.v. on Day 1 (with CHOP) • Cycles 7-8: Gazyva 1,000 mg i.v.	
	Option c: <u>21-days cycles</u> Eight 21-day cycles in combination with CVP	• Cycle 1 (loading doses): 1,000 mg i.v. on Days 1, 8, and 15 (with CVP) • Cycles 2-8: Gazyva 1,000 mg i.v. on Day 1 (with CVP)	
	Maintenance: Every 2 months (after the initial 6-8 cycles)	1,000 mg i.v. every two months as monotherapy	
Exceptions			
Each dose of Gazyva is 1,000 mg administered intravenously with the exception of the first infusions in Cycle 1 of patients with CLL, which are administered on day 1 (100 mg) and day 2 (900 mg).			

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Reference Information

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4. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp.
   i. B-Cell Lymphomas. V5.2022. Revised July 12, 2022.
   ii. Chronic Lymphocytic Leukemia/small lymphocytic lymphoma. V1.2023. Revised August 5, 2022.
7. Park JH, Winer ES, Huntington SF, et al. First line chemo-free therapy with the BRAF inhibitor vemurafenib combined with obinutuzumab is effective in patients with HCL [abstract]. Blood 2021;138:Abstract 43.
8. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial [published correction appears in Lancet Oncol. Lancet Oncol. 2019; 20: 43-56.
9. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with Rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. J Clin Oncol. 2015; 33(30):3467-3474.

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.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Add mantle cell in combination with venetoclax. Add relapsed, refractory, or progressive nodal or splenic marginal zone lymphoma. Modify follicular lymphoma to add Zanubrutinib. Add monotherapy indications. Add relapsed, refractory, or progressive noncutaneous extranodal marginal zone lymphoma. Add relapsed, refractory, or progressive nodal or splenic marginal zone lymphoma. Update may not approve criteria. Coding Reviewed: No changes.	11/18/2024	12/17/2024
Select Review	Update statement for 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.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 10/28/2024