Medical Drug Clinical Criteria

Subject:	Gazyva (obinutuzumab)		
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Overview

This document addresses the use of Gazyva (obinutuzumab). Gazyva is a monoclonal antibody directed against the surface antigen CD20 and is used to treat chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and follicular lymphoma (FL).

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.

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.

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

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.

Clinical Criteria

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.

Gazyva (obinutuzumab)

Requests for Gazyva (obinutuzumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma; **AND**
II. Individual is using for one of the following:
    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, second-line, or subsequent 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 hairy cell leukemia (NCCN 2A); AND
IV. Individual is using as initial therapy who are unable to tolerate purine analogs; AND
V. Individual is using in combination with vemurafenib;

OR

VI. Individual has a diagnosis of Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (NCCN 2A);AND
VII. Individual is unable to tolerate rituximab and rituximab biosimilars;

OR

VIII. Individual has a diagnosis of follicular lymphoma; **AND**
IX. Individual is intolerant to rituximab and is using as a substitute for rituximab; **OR**
X. Individual is using as a single agent in second-line or subsequent therapy; **OR**
XI. 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. Zanubrutinib; **OR**
    E. Lenalidomide;

OR

XII. Individual has a diagnosis of nodal or splenic marginal zone lymphoma (NCCN 2A); **AND**
XIII. Individual is intolerant to rituximab and is using as a substitute for rituximab; **OR**
XIV. 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

OR

XV. Individual has a diagnosis of non-cutaneous extranodal marginal zone lymphoma (NCCN 2A); **AND**
XVI. Individual is intolerant to rituximab and is using as a substitute for rituximab; **OR**
XVII. Individual is using in combination with one of the following regimens:
- A. Bendamustine; **OR**
- B. Lenalidomide;

OR

XVIII. Individual has a diagnosis of extranodal marginal zone lymphoma of the stomach (NCCN 2A); **AND**
XIX. Individual is intolerant to rituximab and is using as a substitute for rituximab; **OR**
XX. Individual is using in combination with one of the following regimens:
- A. Bendamustine; **OR**
- B. Lenalidomide;

OR

XXI. Individual is using as monotherapy for up to 24 months or until disease progression; **AND**
XXII. Individual has one of the following diagnoses:
- A. Follicular Lymphoma; **OR**
- B. Nodal or splenic marginal zone lymphoma; **OR**
- C. Non-cutaneous extranodal marginal zone lymphoma; **OR**
- D. Extranodal marginal zone lymphoma of the stomach;

OR

XXIII. Individual has a diagnosis of Mantle Cell Lymphoma;
AND
- A. Individual is intolerant to rituximab and is using as a substitute for rituximab;
  OR
- B. Individual has classical or indolent TP53 mutated disease; **AND**
- C. Individual is using in combination with venetoclax and zanubrutinib; **AND**
- D. Clinical trials are not available or appropriate for treatment;

OR

XXIV. Individual has a diagnosis of Burkitt Lymphoma, high-grade B-cell lymphomas, HIV-Related B-Cell Lymphomas, Post
XXV. Transplant Lymphoproliferative Disorders, diffuse large B-cell lymphoma, including histologic transformation of indolent lymphomas to Diffuse Large B-Cell Lymphoma, **AND**
- A. Individual is using as pretreatment prior to glofitamab-gxbm administration; **OR**
- B. Individual is intolerant to rituximab and is using as a substitute for rituximab.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9301	Injection, obinutuzumab, 10 mg [Gazyva]

ICD-10 Diagnosis

C82.00-C82.99	Follicular lymphoma

C83.00-C83.09	Small cell B-cell lymphoma
C83.10-C83.19	Mantle cell lymphoma
C83.30-C83.38	Diffuse large B-cell lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.70-C83.79	Burkitt lymphoma
C83.80-C83.89	Other non-follicular lymphoma
C85.10-C85.19	Unspecified B-cell lymphoma
C85.80-C85.89	Other specified types of non-Hodgkin lymphoma
C88.00	Waldenstrom macroglobulinemia not having achieved remission
C88.40	Extranodal marginal zone B-cell lymphoma of mucosa-associated tissue (MALT-lymphoma) not having achieved remission
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
C91.40-C91.42	Hairy cell leukemia
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Document History

Revised: 02/21/2025
Document History:

- 02/21/2025 – Annual Review: Update chronic lymphocytic leukemia/small lymphocytic lymphoma, Add hairy cell leukemia, Add Waldenstrom Macroglobulinemia/lymphoplasmacytic lymphoma, Update follicular lymphoma, Update nodal or splenic marginal zone lymphoma, Update non-cutaneous extranodal marginal zone lymphoma, Add extranodal marginal zone lymphoma of the stomach, Add extranodal marginal zone lymphoma of the stomach to maintenance therapy, Update mantle cell lymphoma, Add B-Cell lymphomas, Update may not approve criteria. Coding Reviewed: Added ICD-10-CM C83.10-C83.19, C83.30-C83.38, C83.398, C83.70-C83.79, C83.80-C83.89, C85.10-C85.19, C85.80-C85.89, C88.00, C88.40, D47.Z1.
- 08/16/2024 – Select Review: add mantle cell in combination with venetoclax, update may not approve criteria. Coding Reviewed: No changes.
- 03/11/2024 – Select Review: add Zanubrutinib combination in follicular lymphoma, format 24 month use to separate section. Coding Reviewed: No changes.
- 02/23/2024 – Annual Review: add criteria for marginal zone lymphomas. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: add hairy cell leukemia indication. Coding Reviewed: Added ICD-10-CM C91.40-C91.42.
- 02/25/2022 – Annual Review: wording and formatting. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: No changes. Coding Reviewed: No changes.
- 11/20/2020 – Select Review: Update chlorambucil combination with NCCN details; add combination use with ibrutinib. Coding Reviewed: No changes.
- 02/21/2020 – Annual Review: Update combination treatment with venetoclax and add combination treatment with Calquence based on Calquence labeling and NCCN recommendations; add TP53 reference for clarity. Coding reviewed: No changes.
- 06/10/2019 – Select Review: Add combination treatment with venetoclax for CLL based on venetoclax labeling and NCCN recommendations. Coding reviewed: No changes.
- 05/17/2019 – Annual Review: First review of Gazyva clinical criteria. Minor wording and formatting changes. Add references for off label criteria. Coding reviewed: No changes.

References

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5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp.
    a. B-Cell Lymphomas. V1.2025. Revised December 20, 2024.
    b. Castleman Disease. V1.2025. Revised December 19, 2024.

c. Chronic Lymphocytic Leukemia/small lymphocytic lymphoma. V1.2025. Revised October 1, 2024.
d. Hairy Cell Leukemia V1.2025. Revised September 26, 2024.
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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.