09-J2000-07

Original Effective Date: 03/15/14

Reviewed: 07/10/19

Revised: 08/15/19

Next Review: 07/08/20

Subject: Obinutuzumab (Gazyva®) Injection

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a mature B-cell lymphoma and comprises approximately 7% of newly diagnosed cases of Non-Hodgkin's Lymphoma (NHL). CLL and SLL are different manifestation of the same disease and are managed in much the same way. The main difference is that in CLL the abnormal lymphocytes are found in bone marrow and blood, while in SLL they are predominately found in the lymph nodes and bone marrow. Treatment options have changed drastically in the last several decades; the introduction of immunotherapeutic agents such as monoclonal antibodies that target cell surface antigens (e.g., CD20, CD52) have led to the development of new and effective regimens that incorporate drugs with different mechanisms of action.

Obinutuzumab (Gazyva) is a humanized monoclonal antibody that binds specifically to the CD20 molecule located on pre B- and mature B-lymphocytes, resulting in cell lysis independent of BCL-2, which potentially circumvents resistance. Obinutuzumab was approved by the U.S. Food and Drug Administration (FDA) in October 2013 for the treatment of previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil. Gazyva was previously granted orphan designation for the treatment of CLL in February 2012. Gazyva also has orphan designations for the treatment of follicular lymphoma (April 2015) and splenic marginal zone lymphoma (June 2015). In February 2016, Gazyva was FDA approved for the treatment of follicular lymphoma in patients who relapsed after or are refractory to a rituximab-containing regimen, in combination with bendamustine followed by obinutuzumab monotherapy. In November 2017, the FDA-approved indication for follicular lymphoma was expanded to include, in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma. While only listed in the labeling for ibrutinib (Imbruvica) (as of February 2019), in

January 2019 ibrutinib's indication of CLL/SLL was expanded to include combination treatment with obinutuzumab based on the positive results of the iLLUMINATE trial in treatment naïve patients, and became the first non-chemotherapy combination regimen for this indication.

Obinutuzumab's safety and effectiveness in CLL leading to initial FDA-approval were evaluated in a 3-arm, open-label trial of patients (n=356; median age: 73 years; 76% with coexisting medical conditions; 68% with CrCl<30 mL/min) with previously untreated CD20+ CLL. Patients were randomly assigned to receive randomized to chlorambucil only, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil. Obinutuzumab 1000 mg IV infusion was administered on days 1, 8, and 15 of the first 28-day cycle and on day 1 of cycles 2 to 6. Chlorambucil 0.5 mg/kg orally was administered on day 1 and day 15 of all six 28-day cycles. Rituximab IV infusion was administered on day 1 of each 28-day cycle with 375 mg/m^2 for cycle 1 and 500 mg/m^2 for cycles 2 to 6. At a median follow-up of 14.2 months, median PFS was significantly improved with obinutuzumab plus chlorambucil compared with chlorambucil alone (23 vs 11.1 months; HR: 0.16; 95% CI: 0.11-0.24; p<0.0001); there were also improvements in overall response rate (75.9% vs 32.1%), complete responses (27.8% vs 0.9%), and median duration of response (15.2 vs 3.5 months). Results for obinutuzumab plus chlorambucil compared with rituximab plus chlorambucil were not reported.

National Comprehensive Cancer Network (NCCN) Guidelines for CLL/SLL (Version 5.2019) list obinutuzumab as first-line therapy for CLL/SLL in the following patient populations: (1) in combination with chlorambucil for disease without del(17p)/TP53 mutation in patients age ≥65 years, younger patients with significant comorbidities, or frail patients unable to tolerate purine analogs (preferred regimen) [category 1]; (2) in combination with bendamustine for disease without del(17p)/TP53 mutation in patients age ≥65 years or for younger patients with or without significant comorbidities who have indications for treatment (preferred regimen) [category 2A]; (3) as a single agent for disease without del(17p)/TP53 mutation in patients age ≥65 years, younger patients with significant comorbidities, or frail patients unable to tolerate purine analogs [category 2B]; and (4) as a single agent for disease **with** del(17p)/TP53 mutation [category 2A]. Obinutuzumab monotherapy is also listed as a treatment option in relapsed or refractory CLL/SLL for all patients without a del(17p) mutation regardless of age or comorbidities [category 2A]. The NCCN Guidelines for B-cell Lymphomas (Version 3.2019) list obinutuzumab in combination with bendamustine, CVP, or CHOP as category 2A recommendations for first-line induction therapy for follicular lymphoma, and include a recommendation for the potential use of obinutuzumab maintenance monotherapy following induction therapy. These same options are also recommended for second-line and subsequent therapy, with the exception that obinutuzumab maintenance monotherapy is only recommended in patients with rituximab-refractory disease. The NCCN recommendations for relapsed, progressive, or refractory marginal zone lymphomas (i.e., gastric MALT, non-gastric MALT, nodal marginal zone, and splenic marginal zone lymphomas) list obinutuzumab in combination with bendamustine followed by maintenance monotherapy as a category 2A recommendation. The guidelines also state that the use of an alternative anti-CD20 monoclonal antibody (e.g., obinutuzumab or ofatumumab) could be used for the treatment of B-cell lymphomas in patients with rare complications to rituximab (e.g., paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis) regardless of histology.

POSITION STATEMENT:

Initiation of obinutuzumab (Gazyva) **meets the definition of medical necessity** when used for any indication listed in Table 1, and all of the indication-specific and maximum-allowable dosage criteria are met

Table 1

Indication	Specific Criteria	Maximum Allowable Dosage
Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)	**ANY** of the following ("1" to "5"): 1. **ALL** of the following ("a", "b", and "c"): a. Use is intended for first-line treatment of previously untreated disease b. Member has the del (17p) mutation c. Obinutuzumab will be used as **EITHER** monotherapy or in combination with venetoclax 2. **ALL** of the following ("a", "b", and "c"): a. Use is intended for first-line treatment of previously untreated disease b. Member does **NOT** have a del (17p) mutation c. Obinutuzumab will be used in combination with bendamustine, or in combination with venetoclax 3. **ALL** of the following ("a", "b", "c", and "d"): a. Use is intended for first-line treatment of previously untreated disease b. Member does **NOT** have a del (17p) mutation c. Obinutuzumab will be used as either monotherapy, or in combination with chlorambucil d. **EITHER** of the following ("i" or "ii"): i. Member is 65 years of age or older ii. Member has significant comorbidity (not able to tolerate purine analogs) 4. **ALL** of the following ("a", "b", and "c"): a. Use is intended for first-line treatment of previously untreated disease b. Obinutuzumab will be used in combination with ibrutinib (Imbruvica) c. **EITHER** of the following ("i" or "ii"): i. Member is 65 years of age or older ii. Member has significant comorbidity (not able to tolerate	First-line therapy in combination with either bendamustine, chlorambucil, or ibrutinib: • Cycle 1 (28-day cycles):100 mg on day 1; 900 mg on day 2; 1,000 mg on day 8; and 1,000 mg on day 15 (i.e., 3,000 mg total in cycle 1) • Cycle 2 to 6 or 8: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 6 cycles of treatment First-line therapy in combination with venetoclax: • Cycle 1 (28-day cycles):100 mg on day 1; 900 mg on day 2; 1,000 mg on day 8; and 1,000 mg on day 15 (i.e., 3,000 mg total in cycle 1) • Cycle 2 to 12: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 12 cycles of treatment Obinutuzumab monotherapy: • Cycle 1 (21-day cycles):100 mg on day 1; 900 mg on day 2; 1,000 mg on day 8; and 1,000 mg on day 15 (i.e., 3,000 mg total in cycle 1) • Cycle 2 to 8: 1,000 mg every 3 weeks (day 1 of each cycle) • Not to exceed 8 cycles of treatment

	purine analogs) 5. **ALL** of the following ("a", "b", and "c"): a. Use is intended for second-line or later treatment of relapsed or refractory disease b. Member does **NOT** have a del (17p) mutation c. Obinutuzumab will be used as monotherapy	
Follicular lymphoma	**EITHER** of the following ("1" or "2"): 1. Obinutuzumab will be used as first-line induction therapy or as second-line or later therapy in combination with **ANY** of the following ("a", "b", or "c"): a. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen b. CVP (cyclophosphamide, vincristine, and prednisone) regimen c. Bendamustine (Bendeka, Treanda) 2. **EITHER** of the following ("a" or "b"): a. Obinutuzumab is being used as maintenance monotherapy for consolidation or extended dosing following first-line induction therapy b. Obinutuzumab is being used as maintenance monotherapy for consolidation or extended dosing following second-line or later therapy **AND** the member has rituximab-refractory disease	<u>In combination with bendamustine</u>: Induction: • Cycle 1 (28-day cycles): 1,000 mg day 1; 1,000 mg day 8; and 1,000 mg day 15 • Cycle 2 to 6: 1,000 mg every 4 weeks (day 1 of each cycle) Maintenance monotherapy (after cycle 6): • 1,000 mg every 8 weeks for 12 doses <u>In combination with CHOP or CVP</u>: Induction: • Cycle 1 (21-day cycles): 1,000 mg day 1; 1,000 mg day 8; and 1,000 mg day 15 • Cycle 2 to 8: 1,000 mg every 3 weeks (day 1 of each cycle) Maintenance monotherapy (after cycle 8): • 1,000 mg every 8 weeks for 12 doses
Gastric mucosa-associated lymphoid tissue (MALT) lymphoma Nodal marginal zone lymphoma	**BOTH** of the following ("1" and "2"): 1. Use is for second-line or subsequent therapy for relapsed, recurrent, or progressive disease 2. **EITHER** of the following ("a" or "b"): a. Obinutuzumab will be used as second-line or later therapy and in combination with bendamustine	Induction: • Cycle 1 (28-day cycles): 1,000 mg day 1; 1,000 mg day 8; and 1,000 mg day 15 • Cycles 2 to 6: 1,000 mg every 4 weeks (day 1 of each cycle) Maintenance monotherapy (after

Non-gastric MALT lymphoma Splenic marginal zone lymphoma	(Bendeka, Treanda) b. Obinutuzumab is being used as maintenance monotherapy for consolidation or extended dosing following second-line or later therapy **AND** the member has rituximab-refractory disease	cycle 6): • 1,000 mg every 8 weeks for 12 doses
Rituximab-intolerance [for an indication not previously listed above]	**ALL** of the following ("1", "2", and "3"): 1. Obinutuzumab is being used as a substitute for rituximab in patients experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis – the specific complication must be provided 2. Member has any of the following conditions: a. AIDS-related B-cell lymphoma b. Burkitt lymphoma c. Castleman's disease d. Diffuse large B-cell lymphoma (DLBCL) [including histologic transformation of marginal zone lymphoma to DLBCL] e. High-grade B-cell lymphoma f. Mantle cell lymphoma g. Post-transplant lymphoproliferative disorder (PTLD) 3. Member meets all medical necessity criteria for their condition as listed in the Rituximab Medical Coverage Guideline (09-J0000-59) [excludes any dosage requirements]	Induction: • Cycle 1 (28-day cycles): 1,000 mg day 1; 1,000 mg day 8; and 1,000 mg day 15 • Cycles 2 to 6: 1,000 mg every 4 weeks (day 1 of each cycle) Maintenance monotherapy (after cycle 6): • 1,000 mg every 8 weeks for 12 doses

Other FDA-approved or NCCN supported diagnosis [not previously listed above]	**EITHER** of the following is met ("1" or "2"): 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation	Maximum FDA-approved dose
Approval duration: 6 months (12 months if for treatment of CLL/SLL in combination with venetoclax)		

The continuation of obinutuzumab (Gazyva) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "5"):

1. Authorization or reauthorization for obinutuzumab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of an indication listed in Table 1 (with the exception of CLL/SLL) or other FDA-approved or NCCN supported diagnosis, **OR** the member previously met **ALL** indication-specific initiation criteria [see initiation criteria for CLL/SLL treatment]
2. The member did **NOT** have disease progression during treatment with obinutuzumab
3. If used as consolidation or extended-dosing maintenance therapy, obinutuzumab is being used as single-agent treatment
4. Dosage does not exceed the following depending on the indication for use and treatment regimen:
    a. Gastric MALT lymphoma, nodal marginal zone lymphoma, non-gastric MALT lymphoma, and splenic marginal zone lymphoma:
        - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
        - After cycle 6: 1,000 mg every 8 weeks
    b. Follicular lymphoma in combination with bendamustine:
        - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
        - After cycle 6: 1,000 mg every 8 weeks
    c. Follicular lymphoma in combination with CHOP or CVP:
        - Cycles 2 to 8 (21-day cycles): 1,000 mg every 3 weeks
        - After cycle 8: 1,000 mg every 8 weeks
    d. Rituximab-intolerance
        - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
        - After cycle 6: 1,000 mg every 8 weeks
    e. Other FDA-approved or NCCN-supported diagnosis (not listed above) - maximum FDA-approved dose

5. Member has not received more than 12 maintenance doses (i.e., doses given after cycle 6 or 8) during their current line of therapy, unless longer dosing is supported in either the FDA-approved prescribing information or NCCN guidelines for the member's specific indication

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). It is also indicated for: (1) in combination with bendamustine followed by obinutuzumab monotherapy, the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen, and (2) in combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.

Obinutuzumab should be administered as an intravenous (IV) infusion; do not administer as an IV push or bolus. Individuals should receive pre-medication (i.e., glucocorticoid, acetaminophen, and an anti-histamine) prior to each obinutuzumab infusion. See the package insert for additional details on infusion rates and rate adjustments.

The recommended dosage for members with CLL/SLL is as follows (1 cycle = 28 days):

- 100 mg on day 1, Cycle 1
- 900 mg on day 2, Cycle 1
- 1,000 mg on day 8 and 15 of Cycle 1
- 1,000 mg on day 1 of Cycles 2 to 6

The recommended dosage for member with relapsed or refractory follicular lymphoma is as follows (1 cycle = 28 days):

- The first 6 cycles are given in combination with bendamustine
    - 1,000 mg on day 1, Cycle 1
    - 1,000 ng on day 8, Cycle 1
    - 1,000 mg on day 15, Cycle 1
    - 1,000 mg on day 1 of Cycles 2 to 6
- After cycle 6 obinutuzumab is given as monotherapy
    - 1,000 mg every 2 months for up to 2 years

The recommended dosage for member with previously untreated follicular lymphoma is as follows – see the product labeling for additional dosing details

- Six 28-day cycles if used in combination with bendamustine
- Six 21-day cycles if used in combination with CHOP, followed by 2 additional 21-day cycles of obinutuzumab alone

- Eight 21-day cycles if used in combination with CVP

Dose Adjustments: Monitor blood counts at regular intervals. Consider treatment interruption if infection, Grade 3 or 4 cytopenia, or Grade 2 or great non-hematologic toxicity occurs.

Drug Availability: obinutuzumab is supplied as a 1,000 mg/40 mL single-use vial.

PRECAUTIONS:

Boxed Warning

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in persons treated with anti-CD-20 antibodies such as obinutuzumab. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment. Discontinue obinutuzumab and concomitant medications in the event of HBV reactivation.
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving obinutuzumab.

Contraindications:

- Patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Precautions/Warnings

- See Boxed Warning
- **Infusion reactions**: Premedicate members with glucocorticoid, acetaminophen and anti-histamine. Monitor members closely during infusions. Interrupt or discontinue infusion for reactions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms.
- **Hypersensitivity Reactions Including Serum Sickness**: Discontinue obinutuzumab permanently.
- **Tumor Lysis Syndrome**: Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for persons with high tumor burden and/or high circulating lymphocyte count. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance.
- **Infections**: Monitor for infection during and after treatment.
- **Neutropenia**: Monitor for infection and promptly treat.
- **Thrombocytopenia**: Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support.
- **Immunization**: Do not administer live virus vaccines prior to or during treatment with obinutuzumab.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J9301	Injection, obinutuzumab, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

B20	Human immunodeficiency virus [HIV] disease

C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.10 – C83.19	Mantle cell lymphoma
C83.30 – C83.39	Diffuse large B-cell lymphoma
C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C83.70 – C83.79	Burkitt lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D36.0	Benign neoplasm of lymph nodes
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Castleman disease
R59.0 – R59.9	Enlarged lymph nodes, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Chronic lymphocytic leukemia (CLL): an indolent (slow-growing) cancer in which too many immature lymphocytes (white blood cells) are found mostly in the blood and bone marrow. Sometimes, in later stages of the disease, cancer cells are found in the lymph nodes and the disease is called small lymphocytic lymphoma.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Autologous Bone Marrow and Stem Cell Transplantation, 02-38241-01

Bendamustine (Treanda), 09-J2000-40

Ibrutinib (Imbruvica), 09-J2000-09

Idelalisib (Zydelig), 09-J2000-23

Interferons for Oncology Use, 09-J1000-37

Lenalidomide (Revlimid), 09-J0000-80

Procarbazine (Matulane), 09-J1000-59

Rituximab (Rituxan), 09-J0000-59

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/10/19.

GUIDELINE UPDATE INFORMATION:

03/15/2014	New Medical Coverage Guideline.
01/01/15	Review and revision to guideline; consisting of annual HCPSC coding update
08/15/15	Review and revision to guideline; consisting of description, position statement, precautions, billing/coding information, related guidelines, and references.
11/01/15	Revision: ICD-9 Codes deleted.
08/15/16	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration section, related guidelines, and references.
12/15/16	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines for CLL/SLL
08/15/17	Review and revision to guideline consisting of updating the description, position statement, and references.
05/15/18	Revision to guideline consisting of updating the description section, position statement, and references based on updated NCCN guidelines for CLL/SLL.
08/15/18	Review and revision to guideline consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding, and references.
03/15/19	Revision to guideline consisting of updating the description section, position statement, billing/coding, and references based on updated NCCN B-Cell Lymphoma guidelines and Imbruvica labeling.

08/15/19	Review and revision to guideline consisting of updating the description section, position statement, and references.