

09-J2000-07

Original Effective Date: 03/15/14

Reviewed: 07/10/24

Revised: 08/15/24

Subject: Obinutuzumab (Gazyva[®]) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

| | | | | | |
|--------------------------------------------|----------------------------------------|--------------------------------|-------------------------------|----------------------------------------|-----------------------------|
| 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. 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. Gazyva was previously granted orphan designation for the treatment of follicular lymphoma in April 2015. While only listed in the labeling for ibrutinib (Imbruvica), 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. Gazyva also has orphan designations, as sponsored by the innovator drug company, for the treatment of membranous nephropathy (June 2020) and for the treatment of childhood-onset idiopathic nephrotic syndrome (NS), defined as steroid dependent or frequently relapsing NS (November 2021).

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/m² for cycle 1 and 500 mg/m² 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 and B-cell Lymphomas list obinutuzumab as a treatment option in various first-line and second-line and later settings as monotherapy and in combination with other treatments. 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 intolerance (including those experiencing severe hypersensitivity reactions requiring discontinuation of rituximab) as well as rare complications to rituximab (e.g., paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesicubullous dermatitis, toxic epidermal necrolysis) regardless of histology. The NCCN Guidelines for Hairy Cell Leukemia list obinutuzumab as useful in certain circumstances in combination with vemurafenib (Zelboraf) as initial therapy for patients with indications for treatment who are unable to tolerate purine analogs including frail patients and those with active infection. Obinutuzumab is recommended as pretreatment prior to the administration of Columvi (glofitamab-gxbm) according to the package labeling for Columvi. Obinutuzumab is administered as a 1,000 mg IV infusion on Cycle 1 Day 1 (i.e., 7 days prior to initiation of Columvi) to deplete circulating and lymphoid tissue B cells and reduce the risk of cytokine release syndrome (CRS). The NCCN B-cell Lymphomas guidelines also include obinutuzumab therapy as a single agent administered prior to fixed-duration glofitamab-gxbm as pretreatment to mitigate CRS.

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 |
|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)</p> | <p>ANY of the following (“1” to “5”):</p> <ol style="list-style-type: none"> 1. ALL of the following (“a”, “b”, and “c”): <ol style="list-style-type: none"> a. Use is intended for first-line treatment of previously untreated disease b. Member HAS the del (17p) mutation c. Obinutuzumab will be used in any of the following regimens: <ol style="list-style-type: none"> i. As monotherapy ii. In combination with venetoclax (Venclexta) iii. In combination with acalabrutinib (Calquence) iv. In combination with high-dose methylprednisolone (HDMP) 2. ALL of the following (“a”, “b”, and “c”): <ol style="list-style-type: none"> 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 any of the following regimens: <ol style="list-style-type: none"> i. In combination with venetoclax (Venclexta) ii. In combination with acalabrutinib (Calquence) iii. In combination with ibrutinib (Imbruvica) iv. In combination with bendamustine v. As monotherapy vi. In combination with chlorambucil* <p style="margin-left: 20px;"><i>*For use in combination with chlorambucil, the member must either be: (1) 65 years of age or older, or (2) have significant comorbidity (creatinine clearance <70 mL/min)</i></p> 3. ALL of the following (“a”, “b”, and “c”): | <p>In combination with either acalabrutinib, bendamustine, chlorambucil, HDMP, or ibrutinib:</p> <ul style="list-style-type: none"> • 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: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 6 cycles of treatment <p>In combination with venetoclax:</p> <ul style="list-style-type: none"> • 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 <p>Obinutuzumab monotherapy:</p> <ul style="list-style-type: none"> • 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 |

| | | |
|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p>a. Use is intended for second-line or later treatment for relapsed or refractory disease</p> <p>b. Member HAS the del (17p) mutation</p> <p>c. Obinutuzumab will be used in any of the following regimens:</p> <ol style="list-style-type: none"> i. In combination with venetoclax (Venclexta) ii. In combination with high-dose methylprednisolone (HDMP) <p>4. ALL of the following (“a”, “b”, and “c”):</p> <p>a. Use is intended for second-line or later treatment for relapsed or refractory disease</p> <p>b. Member does NOT have the del (17p) mutation</p> <p>c. Obinutuzumab will be used in any of the following regimens:</p> <ol style="list-style-type: none"> i. In combination with venetoclax (Venclexta) ii. As monotherapy | <p>(i.e., 3,000 mg total in cycle 1)</p> <ul style="list-style-type: none"> • Cycle 2 to 8: 1,000 mg every 3 weeks (day 1 of each cycle) • Not to exceed 8 cycles of treatment |
| Diffuse large B-cell lymphoma (DLBCL) with histologic transformation from follicular lymphoma | <p>ALL of the following (“1”, “2”, and “3”):</p> <ol style="list-style-type: none"> 1. Member has coexisting extensive follicular lymphoma 2. Member achieved a complete response to chemoimmunotherapy 3. Obinutuzumab is being used as maintenance monotherapy | 1,000 mg every 8 weeks for 12 doses |
| Follicular lymphoma [a.k.a., classical follicular lymphoma] | <p>ANY of the following (“1”, “2”, or “3”):</p> <ol style="list-style-type: none"> 1. Obinutuzumab will be used as first-line induction therapy or as second-line or later therapy (if not previously given) in combination with ANY of the following (“a”, “b”, “c”, or “d”): <ol style="list-style-type: none"> a. Bendamustine b. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen c. CVP (cyclophosphamide, vincristine, and prednisone) regimen d. Lenalidomide (Revlimid) 2. Obinutuzumab will be used as third-line or later therapy (i.e., after two or more lines of systemic | <p>In combination with bendamustine or lenalidomide:</p> <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> |

| | | |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p>therapy) AND will be given in combination with zanubrutinib (Brukinsa)</p> <p>3. EITHER of the following (“a” or “b”):</p> <p>a. Obinutuzumab is being used as maintenance monotherapy for consolidation or extended dosing following first-line induction therapy</p> <p>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</p> | <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses <p>In combination with CHOP or CVP:</p> <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 8):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses <p>In combination with zanubrutinib:</p> <ul style="list-style-type: none"> • 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) • After cycle 6: 1,000 mg every 8 weeks for 12 doses |
| <p>Hairy cell leukemia</p> | <p>ALL of the following (“1” to “3”):</p> <ol style="list-style-type: none"> 1. Use is intended for first-line treatment of previously untreated disease 2. Member is unable to tolerate purine analogs such as cladribine or pentostatin (for example, frail patients and those with active infections) 3. Obinutuzumab will be used in combination with vemurafenib (Zelboraf) | <ul style="list-style-type: none"> • Cycle 1 (28-day cycles): 1,000 mg day 1; 1,000 mg, day 8; and 1,000 mg day 15 • Cycles 2 to 3: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 3 cycles of treatment |
| <p>Mantle cell lymphoma</p> | <p>ALL of the following (“1” to “4”):</p> <ol style="list-style-type: none"> 1. Use is intended as first-line induction therapy for previously untreated disease | <ul style="list-style-type: none"> • 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 |

| | | |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <ol style="list-style-type: none"> 2. Member has TP53 mutated disease 3. Provider attests that the member is unable to enroll in a clinical trial for treatment [a clinical trial is strongly recommended by the NCCN when available] 4. Obinutuzumab will be used in combination with both venetoclax (Venclexta) and zanubrutinib (Brukinsa) | <p>(i.e., 3,000 mg total in cycle 1)</p> <ul style="list-style-type: none"> • Cycle 2 to 8: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 8 cycles of treatment |
| <p>Nodal marginal zone lymphoma</p> | <p>EITHER of the following (“1” or “2”):</p> <ol style="list-style-type: none"> 1. Obinutuzumab will be used as first-line induction therapy in combination with ANY of the following (“a”, “b”, or “c”): <ol style="list-style-type: none"> a. Bendamustine b. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen c. CVP (cyclophosphamide, vincristine, and prednisone) regimen 2. BOTH of the following (“a” and “b”): <ol style="list-style-type: none"> a. Use is for second-line or subsequent therapy for relapsed, recurrent, or progressive disease b. ANY of the following (“i”, “ii”, or “iii”): <ol style="list-style-type: none"> i. Obinutuzumab will be used in combination with bendamustine AND the member has not been previously treated with bendamustine ii. Obinutuzumab will be used in combination with lenalidomide (Revlimid) iii. Obinutuzumab is being used as maintenance monotherapy for extended dosing following second-line or later therapy AND the member has rituximab-refractory disease | <p>In combination with bendamustine or lenalidomide:</p> <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses <p>In combination with CHOP or CVP:</p> <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 8):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses |

| | | |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Extranodal marginal zone lymphoma of the stomach [a.k.a., gastric mucosa-associated lymphoid tissue (MALT) lymphoma]</p> | <p>BOTH of the following (“1” and “2”):</p> <ol style="list-style-type: none"> 1. Use is for second-line or subsequent therapy for relapsed, recurrent, or progressive disease 2. ANY of the following (“a”, “b”, or “c”): <ol style="list-style-type: none"> a. Obinutuzumab will be used in combination with bendamustine AND the member has not been previously treated with bendamustine b. Obinutuzumab will be used in combination with lenalidomide (Revlimid) c. Obinutuzumab is being used as maintenance monotherapy for extended dosing following second-line or later therapy AND the member has rituximab-refractory disease | <p>In combination with bendamustine or lenalidomide:</p> <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses |
| <p>Extranodal marginal zone lymphoma (EMZL) of non-gastric sites (noncutaneous) [a.k.a., non-gastric MALT lymphoma]</p> | | |
| <p>Splenic marginal zone lymphoma</p> | | |
| <p>Pretreatment prior to the administration of Columvi (glofitamab-gxbm)</p> | <p>BOTH of the following (“1” and “2”):</p> <ol style="list-style-type: none"> 1. Member will be or is currently receiving treatment with Columvi (glofitamab-gxbm) 2. EITHER of the following (“a” or “b”): <ol style="list-style-type: none"> a. Obinutuzumab is being administered as an IV infusion on Cycle 1 Day 1 (i.e., 7 days prior to initiation of Columvi) to deplete circulating and lymphoid tissue B cells and reduce the risk of cytokine release syndrome (CRS) b. Obinutuzumab is being administered as an IV infusion to deplete circulating and lymphoid tissue B cells and reduce the risk of CRS, AND there has been an unintended extended gap between Columvi doses as follows: <ul style="list-style-type: none"> • >4 weeks after the initial 2.5 mg step-up dose • >6 weeks after the second 10 mg step-up dose | <p>1,000 mg given as a single dose</p> |

| | | |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <ul style="list-style-type: none"> • >6 weeks after any 30 mg maintenance dose | |
| Rituximab-intolerance | <p>ALL of the following (“1”, “2”, and “3”):</p> <ol style="list-style-type: none"> 1. Obinutuzumab is being used as a substitute for rituximab in patients with intolerance (including those experiencing severe hypersensitivity reactions requiring discontinuation of rituximab) as well as rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis – the specific intolerance or complication must be provided 2. Member has any of the following conditions: <ol style="list-style-type: none"> a. Burkitt lymphoma b. Castleman's disease c. Diffuse large B-cell lymphoma (DLBCL) [including histologic transformation of an indolent lymphoma to DLBCL] d. Extranodal marginal zone lymphoma (EMZL) of non-gastric sites (noncutaneous) e. Extranodal marginal zone lymphoma of the stomach f. High-grade B-cell lymphomas g. HIV-related B-cell lymphoma h. Follicular lymphoma i. Mantle cell lymphoma j. Nodal marginal zone lymphoma k. Post-transplant lymphoproliferative disorder (PTLD) l. Splenic marginal zone lymphoma 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] | <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses |
| Membranous nephropathy | <p>BOTH of the following (“1” and “2”):</p> | <p>Induction:</p> |

| | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [orphan indication] | <ol style="list-style-type: none"> 1. Member meets ONE of the following: <ol style="list-style-type: none"> a. eGFR less than or equal to 60 ml/min/1.73 m² b. Proteinuria greater than or equal to 3.5 g/day and no decrease greater than 50% after 6 months of therapy with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) c. Proteinuria greater than 8 g/day for 6 months 2. Member has had an inadequate response to treatment with rituximab | <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> <ul style="list-style-type: none"> • 1,000 mg every 8 weeks for 12 doses |
| Pediatric idiopathic nephrotic syndrome [orphan indication] | BOTH of the following (“1” and “2”): <ol style="list-style-type: none"> 1. Member’s disease is dependent on or refractory to corticosteroids 2. Member has had an inadequate response to treatment with rituximab | <p>Induction:</p> <ul style="list-style-type: none"> • 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) <p>Maintenance monotherapy (after cycle 6):</p> <ul style="list-style-type: none"> • 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”): <ol style="list-style-type: none"> 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 are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation | Maximum FDA-approved dose or NCCN recommend dose |
| Approval duration: 6 months (12 months if for treatment of CLL/SLL in combination with venetoclax, mantle cell lymphoma, or DLBCL with histologic transformation from follicular lymphoma) | | |

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 exceptions of CLL/SLL, hairy cell leukemia, mantle cell lymphoma, and pretreatment prior to the administration of Columvi - see initiation criteria) 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. DLBCL with histologic transformation from follicular lymphoma
 - 1,000 mg every 8 weeks
 - b. Extranodal marginal zone lymphoma (EMZL) of non-gastric sites (noncutaneous), extranodal marginal zone lymphoma of the stomach, and splenic marginal zone lymphoma in combination with bendamustine or lenalidomide:
 - 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 bendamustine, lenalidomide, or zanubrutinib:
 - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
 - After cycle 6: 1,000 mg every 8 weeks
 - d. 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
 - e. Membranous nephropathy
 - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
 - After cycle 6: 1,000 mg every 8 weeks
 - f. Nodal marginal zone lymphoma in combination with bendamustine or lenalidomide:
 - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
 - After cycle 6: 1,000 mg every 8 weeks
 - g. Nodal marginal zone 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
 - h. Pediatric idiopathic nephrotic syndrome
 - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
 - After cycle 6: 1,000 mg every 8 weeks

- i. Rituximab-intolerance
 - Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
 - After cycle 6: 1,000 mg every 8 weeks
 - j. Other FDA-approved or NCCN-supported diagnosis (not listed above) - maximum FDA-approved dose or NCCN recommend 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 antihistamine) 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 greater 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 patients with glucocorticoid, acetaminophen and antihistamine. Monitor patients closely during infusions. Interrupt, reduce rate, or discontinue infusion for infusion-related reactions based on severity.
- **Hypersensitivity Reactions Including Serum Sickness:** Discontinue obinutuzumab permanently.
- **Tumor Lysis Syndrome:** Premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count, or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance.

- **Infections:** Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.
- **Neutropenia:** In patients with Grade 3 to 4 neutropenia, monitor laboratory tests until resolution and for infection. Consider dose delays and infection prophylaxis, as appropriate.
- **Thrombocytopenia:** Monitor for decreased platelet counts and bleeding. Transfusion may be necessary.
- **Disseminated Intravascular Coagulation (DIC):** Evaluate cause and monitor for bleeding, thrombosis, and need for supportive care.
- **Immunization:** Avoid administration of live virus vaccines during obinutuzumab treatment and until B-cell recovery.
- **Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, obinutuzumab can cause B-cell depletion in infants exposed to obinutuzumab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving obinutuzumab and for 6 months after the last dose.

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 |
| C91.40 | Hairy cell leukemia not having achieved remission |
| C91.42 | Hairy cell leukemia in relapse |
| D36.0 | Benign neoplasm of lymph nodes |
| D47.Z1 | Post-transplant lymphoproliferative disorder (PTLD) |
| D47.Z2 | Castleman disease |
| N04.0 – N04.9 | Nephritic syndrome |
| N05.0 – N05.9 | Unspecified nephritic syndrome |
| R59.0 – R59.9 | Enlarged lymph nodes, unspecified |
| Z29.89 | Encounter for other specified prophylactic measures [for Columvi pretreatment indication only] |

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: Florida Blue 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 HCl Injection, 09-J2000-40](#)

[Ibrutinib \(Imbruvica\), 09-J2000-09](#)

Oral Oncology Medications, 09-J3000-65

Rituximab Products, 09-J0000-59

OTHER:

None

REFERENCES:

1. Brukinsa (zanubrutinib capsule) [package insert]. BeiGene USA, Inc. San Mateo (CA): June 2024.
2. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. *Blood*. 2016 Jan 7;127(1):79-86.
3. Calquence (acalabrutinib capsules) [package insert]. AstraZeneca Pharmaceuticals; Wilmington, DE. June 2023.
4. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014 Oct 2;124(14):2196-202.
5. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2024. Available at: <https://www.clinicalkey.com/pharmacology/>. Accessed 06/21/24.
6. Columvi (glofitamab solution, concentrate) [package insert]. Genentech, Inc. South San Francisco (CA): June 2023.
7. DRUGDEX System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2024 Jun 21].
8. Gazyva (Obinutuzumab) [package insert]. Genentech, Inc. South San Francisco (CA): July2022.
9. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014;370(12):1101-1110.
10. Imbruvica (ibrutinib) [package insert]. Pharmacyclics LLC. Sunnyvale (CA): May 2024.
11. Merli M, Ferrario A, Basilico C, et al. Novel agents in indolent lymphomas. *Ther Adv Hematol*. 2013 Apr;4(2):133-48.
12. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 06/21/24.
13. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. B-cell Lymphomas (Version 2.2024 - April 30, 2024) [cited 2024 Jun 21]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
14. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Chronic Castleman Disease (Version 1.2024 – January 18, 2024) [cited 2024 Jun 28]. Available at https://www.nccn.org/professionals/physician_gls/pdf/castleman.pdf.
15. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 3.2024 - March 26, 2024) [cited 2024 Jun 21]. Available at https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

16. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Hairy Cell Leukemia (Version 2.2024 - April 22, 2024) [cited 2024 Jun 21] Available at https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf.
17. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Jun 21]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index>.
18. 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.
19. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013 Aug 15;122(7):1137-43. Epub 2013 Jul 10.
20. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Jun 23. pii: S1470-2045(16)30097-3.
21. Sharman JP, Yimer HA, Boxer M, et al. Results of a phase II multicenter study of obinutuzumab plus bendamustine in pts with previously untreated chronic lymphocytic leukemia (CLL). J Clin Oncol. 2017;35(15 suppl).
22. Trautmann A, Vivarelli M, Samuel S, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2020; 35:1529.
23. Venclexta (venetoclax) [package insert]. AbbVie Inc. North Chicago, IL, June 2022.
24. Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: A phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. J Clin Oncol 2023; 41:5107-5117.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/10/24.

GUIDELINE UPDATE INFORMATION:

| | |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03/15/14 | 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. |
| 03/15/20 | Revision to guideline consisting of updating the description section, position statement, related guidelines, and references based on updated NCCN guidelines. |
| 08/15/20 | Review and revision to guideline consisting of updating the position statement, precautions, related guidelines, and references. |
| 08/15/21 | Review and revision to guideline consisting of updating the position statement, precautions, related guidelines, and references. |
| 08/15/22 | Review and revision to guideline consisting of updating the description section, position statement, billing/coding, and references. |
| 08/15/23 | Review and revision to guideline consisting of updating the description section, position statement, precautions, billing/coding, and references. Added new indication of hairy cell leukemia. Updated the positioning of regimens for CLL/SLL. |
| 02/15/24 | Revision to guideline consisting of updating the description, position statement, billing/coding, and references. Added allowance for the use of obinutuzumab as a single dose as pretreatment prior to the use of Columvi (glofitamab-gxbm). |
| 04/15/24 | Revision to guideline consisting of updating the description, position statement, and references. For follicular lymphoma, added obinutuzumab + zanubrutinib (Brukinsa) as a third-line or later therapy based on updated NCCN guidelines and new FDA-approved indication for Brukinsa. |
| 08/15/24 | Review and revision to guideline consisting of updating the description section, position statement, and references. Added a new indication of mantle cell lymphoma. Updated the CLL/SLL section for better clarity and added high-dose methylprednisolone (HDMP) + obinutuzumab as a treatment option in certain situations. |