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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. 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. In October 2025, the FDA approved the first non-oncology indication for Gazyva. The indication is the treatment of adult patients with active lupus nephritis (LN) who are receiving standard therapy. 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 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 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, vesiculobullous dermatitis, toxic epidermal necrolysis) regardless of histology. The CLL/SLL guidelines also include a section for Richter transformation (CLL/SLL transformed into DLBCL) in which the combination of venetoclax + atezolizumab + obinutuzumab is listed as a non-chemoimmunotherapy (CIT) based regimen. 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 monotherapy is also listed as an option for relapsed/refractory hairy cell leukemia. 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.

The efficacy and safety of obinutuzumab leading to FDA-approval for active lupus nephritis was evaluated in REGENCY (NCT04221477), a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in 271 patients with ISN/RPS 2003 Class III or IV, with or without concomitant Class V lupus nephritis (LN) (confirmed by biopsy), treated with standard therapy consisting of mycophenolate mofetil (MMF) and corticosteroids. Patients were randomized 1:1 to receive obinutuzumab 1,000 mg (n=135) or placebo (n=136) intravenously, in combination with MMF 2 to 2.5 g/day and a tapering course of corticosteroids and were evaluated over 76 weeks. All patients received oral prednisone 0.5 mg/kg/day (maximum 60 mg/day) and remained at this dose until Week 2. Beginning on Day 15, prednisone was tapered to achieve a target dose of 5 mg/day by Week 24. Prednisone was maintained at a low dose (5 mg/day) from Week 24 until Week 80. The primary endpoint measure was proportion of patients who achieved complete renal response (CRR) at Week 76, defined as meeting all of the following criteria: UPCR <0.5 g/g; eGFR ≥85% of baseline, as calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; with no occurrence of the following intercurrent events: rescue therapy, treatment failure, death or early study withdrawal. The proportion of patients achieving CRR at Week 76 was significantly greater in patients treated with obinutuzumab in combination with standard therapy (46.4%) vs. patients who received placebo plus standard therapy (33.1%). There were also a higher proportion of patients who achieved CRR with successful prednisone taper at Week 76 (42.7% vs. 30.9%) and proteinuric response at Week 76 (55.5% vs. 41.9%). In addition, patients who received obinutuzumab were less likely to experience the outcome of "renal-related event or death" compared with placebo (17.8% vs. 33.8%).

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 in any of the following regimens: i. As monotherapy ii. In combination with venetoclax (Venclexta) iii. In combination with acalabrutinib (Calquence) iv. In combination with both acalabrutinib and venetoclax v. In combination with high-dose methylprednisolone (HDMP) 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 any of the following regimens: i. In combination with venetoclax (Venclexta) ii. In combination with acalabrutinib (Calquence) iii. In combination with both acalabrutinib and venetoclax iv. In combination with ibrutinib (Imbruvica) v. In combination with bendamustine vi. As monotherapy vii. In combination with chlorambucil* **For use in combination with chlorambucil, the member must either be: (1) 65 years of age or older, or (2) have significant*	In combination with either acalabrutinib, acalabrutinib + venetoclax, bendamustine, chlorambucil, HDMP, 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: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 6 cycles of treatment 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

	comorbidity (creatine clearance <70 mL/min) 3. **ALL** of the following ("a", "b", and "c"): a. Use is intended for second-line or later treatment for relapsed or refractory disease b. Member **HAS** the del (17p) mutation c. Obinutuzumab will be used in any of the following regimens: i. In combination with venetoclax (Venclexta) ii. In combination with high-dose methylprednisolone (HDMP) iii. As monotherapy 4. **ALL** of the following ("a", "b", and "c"): a. Use is intended for second-line or later treatment for relapsed or refractory disease b. Member does **NOT** have the del (17p) mutation c. Obinutuzumab will be used in any of the following regimens: i. In combination with venetoclax (Venclexta) ii. As monotherapy	(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
Diffuse large B-cell lymphoma (DLBCL) with histologic transformation from follicular lymphoma	**ALL** of the following ("1", "2", and "3"): 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., classic follicular lymphoma]	**ANY** of the following ("1", "2", or "3"): 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"): a. Bendamustine b. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen c. CVP (cyclophosphamide, vincristine, and prednisone) regimen d. Lenalidomide 2. Obinutuzumab will be used as third-line or later therapy (i.e., after two or more lines of systemic	In combination with bendamustine or lenalidomide: 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):

	therapy) **AND** will be given in combination with zanubrutinib (Brukinsa) 3. **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	• 1,000 mg every 8 weeks for 12 doses In combination with CHOP or CVP: 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 In combination with zanubrutinib: • 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
Hairy cell leukemia	**EITHER** of the following ("1" or "2"): 1. **ALL** of the following ("a", "b", and "c"): a. Use is intended for first-line treatment of previously untreated disease b. Member is unable to tolerate purine analogs such as cladribine or pentostatin (for example, frail patients and those with active infections) c. Obinutuzumab will be used in combination with vemurafenib (Zelboraf) 2. **BOTH** of the following: a. Use is intended for second-line or later treatment of previously treated disease b. Obinutuzumab is being used as monotherapy	First-line treatment: • 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 Second-line or later treatment: • 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) • Not to exceed 6 cycles of treatment
Lupus nephritis (LN)	**ALL** of the following ("1" to "6"): 1. Member has a diagnosis of systemic lupus erythematosus (SLE) as confirmed by laboratory testing demonstrated the presence of autoantibodies [e.g., antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Smith (anti-Sm) antibodies, anti-Ro/SSA antibodies, anti-La/SSB antibodies] 2. Member has biopsy-proven lupus nephritis (LN) of International Society of Nephrology/ Renal Pathology Society (ISN/RPS) class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with or without coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis – documentation of the biopsy results must be provided 3. Obinutuzumab will be used in combination with standard lupus nephritis therapy which must include **BOTH** of the following (a'" and "b"): a. A corticosteroid (includes any tapering doses of corticosteroids) b. **ANY** of the following non-biologic immunosuppressants: • azathioprine • cyclophosphamide • leflunomide • mycophenolate mofetil or mycophenolate sodium 4. Obinutuzumab is prescribed by, or in consultation with, a nephrologist or rheumatologist 5. Member is 18 years of age or older 6. Obinutuzumab will **NOT** be used in combination with anifrolumab (Saphnelo), belimumab (Benlysta), rituximab, or voclosporin (Lupkynis)	Initial dosing: • 1,000 mg on week 0 (first dose), and then 1,000 mg on week 2 and week 24 Maintenance dosing: • 1,000 mg on week 26, and then 1,000 every 6 months thereafter
Mantle cell lymphoma	**ALL** of the following ("1" to "4"): 1. Use is intended as first-line induction therapy for previously untreated disease 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	• 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)

	is strongly recommended by the NCCN when available] 4. Obinutuzumab will be used in combination with both venetoclax (Venclexta) and zanubrutinib (Brukinsa)	• Cycle 2 to 8: 1,000 mg every 4 weeks (day 1 of each cycle) • Not to exceed 8 cycles of treatment
Nodal marginal zone lymphoma	**EITHER** of the following ("1" or "2"): 1. Obinutuzumab will be used as first-line induction therapy in combination with **ANY** of the following ("a", "b", or "c"): 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"): a. Use is for second-line or subsequent therapy for relapsed, recurrent, or progressive disease b. **ANY** of the following ("i", "ii", or "iii"): 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 iii. Obinutuzumab is being used as maintenance monotherapy for extended dosing following second-line or later therapy **AND** the member has rituximab-refractory disease	In combination with bendamustine or lenalidomide: 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 In combination with CHOP or CVP: 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
Extranodal marginal zone lymphoma of the stomach [a.k.a., gastric mucosa-associated lymphoid tissue (MALT) lymphoma]	**BOTH** of the following ("1" and "2"): 1. Use is for second-line or subsequent therapy for relapsed, recurrent, or progressive disease 2. **ANY** of the following ("a", "b", or "c"): a. Obinutuzumab will be used in combination with bendamustine **AND** the member has not been previously treated with bendamustine	In combination with bendamustine or lenalidomide: Induction: • Cycle 1 (28-day cycles): 1,000 mg day 1; 1,000 mg day 8; and 1,000 mg day 15

Extranodal marginal zone lymphoma (EMZL) of non-gastric sites (noncutaneous) [a.k.a., non-gastric MALT lymphoma] Splenic marginal zone lymphoma	b. Obinutuzumab will be used in combination with lenalidomide c. Obinutuzumab is being used as maintenance monotherapy for extended dosing following second-line or later therapy **AND** the member has rituximab-refractory disease	• 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
Pretreatment prior to the administration of Columvi (glofitamab-gxbm)	**BOTH** of the following ("1" and "2"): 1. Member will be or is currently receiving treatment with Columvi (glofitamab-gxbm) 2. **EITHER** of the following ("a" or "b"): 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: • >4 weeks after the initial 2.5 mg step-up dose • >6 weeks after the second 10 mg step-up dose • >6 weeks after any 30 mg maintenance dose	1,000 mg given as a single dose
Richter transformation (CLL/SLL transformed to DLBCL)	**BOTH** of the following ("1" and "2"): 1. Member has biopsy-confirmed transformation of CLL/SLL to diffuse large B-cell lymphoma (DLBCL) 2. Obinutuzumab will be used in combination with **BOTH** venetoclax (Venclexta) **AND** either atezolizumab (Tecentriq) or atezolizumab-hyaluronidase (Tecentriq Hybreza)	• 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
Rituximab-intolerance	**ALL** of the following ("1", "2", and "3"): 1. Obinutuzumab is being used as a substitute for rituximab in patients with intolerance (including those experiencing severe hypersensitivity	Induction: • Cycle 1 (28-day cycles): 1,000 mg day

	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: 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]	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
Membranous nephropathy [orphan indication]	**BOTH** of the following ("1" and "2"): 1. Member meets **ONE** of the following: a. eGFR less than or equal to 60 ml/min/1.73 m^2 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	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
Pediatric idiopathic	**BOTH** of the following ("1" and "2"):	Induction:

nephrotic syndrome [orphan indication]	1. Member's disease is dependent on or refractory to corticosteroids 2. Member has had an inadequate response to treatment with rituximab	• 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 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, Richter transformation, 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
2. **EITHER** of the following depending on the indication for use:
    a. Lupus nephritis – the member has had a beneficial response to treatment with obinutuzumab
    b. Other indications - 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*

    **Does not apply to the indication of lupus nephritis*
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. Lupus nephritis:
- 1,000 mg every 6 months

f. Membranous nephropathy:
- 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 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

h. 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

i. 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

j. Rituximab-intolerance:
- Cycles 2 to 6 (28-day cycles): 1,000 mg every 4 weeks
- After cycle 6: 1,000 mg every 8 weeks

k. 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

   **Does not apply to the indication of lupus nephritis*

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: Obinutuzumab is indicated for the following, (1) in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL), (2) 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, (3) 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, and (4) the treatment of adult patients with active lupus nephritis (LN) who are receiving standard therapy.

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

The recommended dosage for member with active lupus nephritis (LN) who are receiving standard therapy is as follows– see the product labeling for additional dosing details:

- Initial dosing - 1,000 mg on week 0 (first dose) and then 1,000 mg on week 2 and week 24
- Maintenance dosing - 1,000 mg on week 26 and then 1,000 every 6 months thereafter

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

WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients receiving CD20-directed cytolytic antibodies, including obinutuzumab. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with obinutuzumab. 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, including 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**: In CLL and FL, 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.
- **Serious, Including Fatal, 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 – C83.398	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
M32.14	Glomerular disease in systemic lupus erythematosus
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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

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.

Systemic lupus erythematosus: a systemic autoimmune disease than can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage.

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

Lupus, 09-J5000-51

Oncology Self-Administered Medications, 09-J3000-65

Rituximab Products, 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 07/08/26.

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.
10/01/24	Revision: ICD-10 code updates.
08/15/25	Review and revision to guideline consisting of updating the position statement and references.
01/15/26	Revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, related guidelines, and references. New FDA-approved indication for the treatment of adult patients with active lupus nephritis who are receiving standard therapy.
08/15/26	Review and revision to guideline consisting of updating the description, position statement and references. New NCCN supported uses.