Draft Revised Policy: Do Not Implement

Obinutuzumab (Gazyva®)

DESCRIPTION

Obinutuzumab is a monoclonal antibody which targets the CD20 antigen expressed on the surface of B-lymphocytes, both pre B-lymphocytes and mature B-lymphocytes. When obinutuzumab binds with the CD20 antigen it causes B-cell lysis and cell death likely through three ways. First, it causes engagement of immune effector cells; second, it directly activates intracellular death signaling pathways; third, activation of the complement cascade. Once engaged, the immune effector cells mechanisms of cell death include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

POLICY

- Obinutuzumab for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
  - B Cell Lymphomas
- Obinutuzumab for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

The proposal is to add text/statements in red and to delete text/statements with strikethrough:

INITIAL APPROVAL CRITERIA

- Patient is at least 18 years of age; **AND**

Universal Criteria

- Patient does not have an active infection, including clinically important localized infections; **AND**
- Patient has not received a live vaccine within 28 days prior to starting treatment and live vaccines will not be administered concurrently while on treatment; **AND**
- Patient has been screened for the presence of hepatitis B (HBV) infection (i.e., HBsAg and anti-HBc) prior to initiating therapy and patients with evidence of current or prior HBV infection will be monitored for HBV reactivation during treatment; **AND**

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

- Used as first-line therapy; **AND**
  - Used in combination with chlorambucil; **OR**
  - Used in combination with acalabrutinib; **OR**
  - Used in combination with venetoclax; **OR**
  - Used as single agent therapy for disease with del(17p)/TP53 mutation; **OR**
  - Used in combination with bendamustine for disease without del(17p)/TP53 mutation (excluding use in frail patients with significant comorbidity [i.e., not able to tolerate purine analogs]); **OR**
- Used for as subsequent therapy; **AND**
  - Used as single agent therapy for disease without del(17p)/TP53 mutation

B-Cell Lymphomas

- Follicular Lymphoma (Grade 1-2)
  - Used as first-line therapy; **AND**

        - Used in combination with chemotherapy [e.g., bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone)]; **OR**
    - Used as subsequent therapy, if not previously used as first-line therapy, for refractory or progressive disease; **AND**
        - Used in combination with chemotherapy [e.g., bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone)]; **OR**
        - Used as a single agent; **OR**
        - Used in combination with lenalidomide; **OR**
    - Used as a single agent for maintenance therapy; **AND**
        - Used as first-line consolidation therapy or extended dosing following chemoimmunotherapy; **OR**
        - Used as second-line consolidation therapy or extended dosing in patients who are refractory to rituximab; **OR**
        - Used in patients with histologic transformation to diffuse-large B-cell lymphoma with extensive co-existing follicular lymphoma who achieve a complete response to chemoimmunotherapy; **OR**
    - Used as a substitute for rituximab in patients with intolerance or experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis
- MALT Lymphoma (Gastric or Non-Gastric) or Marginal Zone Lymphoma (Splenic or Nodal)
    - Used as first-line therapy (Nodal Marginal Zone Lymphoma only); **AND**
        - Used in combination with chemotherapy [e.g., bendamustine or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CVP (cyclophosphamide, vincristine, prednisone)]; **OR**
    - Used in combination with bendamustine; **AND**
        - Used as subsequent therapy, if not previously treated with bendamustine, for recurrent disease after prior treatment with rituximab *(Splenic Marginal Zone Lymphoma only)*; **OR**
        - Used as subsequent therapy, if not previously treated with bendamustine, for relapsed ~~recurrent~~ or progressive disease (Gastric MALT Lymphoma only); **OR**
        - Used as subsequent therapy, if not previously treated with bendamustine, for refractory or progressive disease (*Nodal Marginal Zone Lymphoma only)*; **OR**
        - Used as subsequent therapy, if not previously treated with bendamustine, for recurrent or progressive disease *(Non-Gastric MALT Lymphoma only)*; **OR**
    - Used as a single agent for maintenance therapy as second-line consolidation or extended dosing in rituximab refractory patients treated with obinutuzumab and bendamustine for recurrent disease; **OR**
    - Used as a substitute for rituximab in patients with intolerance or experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis
- Histologic Transformation of Nodal Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, High Grade B-Cell Lymphomas, Burkitt Lymphoma, AIDS Related B Cell Lymphomas, Post-Transplant Lymphoproliferative Disorders, or Castleman's Disease
    - Used as a substitute for rituximab in patients with intolerance or experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis

RENEWAL CRITERIA

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in Initial Approval Criteria; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe neutropenia/febrile neutropenia, severe thrombocytopenia, severe infusion-related reactions, hypersensitivity

reactions including serum sickness, tumor lysis syndrome (TLS), serious bacterial, fungal, or viral infections, etc.; **AND**
- Patient has been evaluated for the presence of progressive multifocal leukoencephalopathy (PML) and has been found to be negative; **AND**

CLL/SLL

- Authorizations may **NOT** be renewed

Maintenance treatment of B-Cell Lymphomas

- Length of therapy does not exceed 2 years

DOSAGE/ADMINISTRATION

INDICATION	DOSE
CLL/SLL	Combination therapy: • 100 mg day 1, 900 mg day 2, then 1000 mg days 8 and 15 of cycle 1 (loading doses) • 1000 mg on Day 1 of cycles 2-6 (28-day cycle) Monotherapy: • 100 mg day 1, 900 mg day 2, then 1000 mg days 8 and 15 of cycle 1 (loading doses) • 1000 mg on Day 1 of cycles 2-8 (21-day cycle) -OR- • 100mg day 1, 900 mg day 2, 1000 mg day 3, 2000 mg day 8 and 15 of cycle 1 (loading doses) • 2000 mg on Day 1 of cycles 2-8 (21-day cycle)

B-Cell Lymphomas	Initial Combination therapy:
	• 1000 mg days 1, 8, & 15 of cycle 1 (loading doses); given in combination with chemotherapy or lenalidomide
	  ○ Combination chemotherapy:
	  ▪ 1000 mg day 1 of cycles 2-6 (28-day cycle) in combination with bendamustine
	  ▪ 1000 mg day 1 of cycles 2-6 (21-day cycle) in combination with CHOP, followed by 2 additional 21-day cycles of Gazyva alone
	  ▪ 1000 mg day 1 of cycles 2-8 (21-day cycle) with CVP
	  ○ In combination with lenalidomide:
	  ▪ 1000 mg day 1 of cycles 2-6 (28-day cycle)
	Initial Monotherapy:
	• 1000 mg once a week for 4 weeks on days 1, 8, 15, & 22
	Maintenance therapy for use after initial combination therapy or monotherapy:
	• 1000 mg every 2 months for up to two years as monotherapy
	• **NOTE:** When initial therapy is given in combination with lenalidomide, the first year of maintenance therapy will be given with lenalidomide, followed by an additional year of monotherapy

LENGTH OF AUTHORIZATION

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) combination therapy:
- Coverage is provided for six 28-day cycles (6 months) and may NOT be renewed.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) monotherapy:

- Coverage is provided for eight 21-day cycles (6 months) and may NOT be renewed.

All other indications:
- Coverage is provided for six months and may be renewed for up to a maximum of two years of maintenance therapy.

DOSING LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL):
Loading Dose:
- 10 billable units day 1, 90 billable units day 2, 100 billable units day 3, 200 billable units days 8 and 15 of Cycle 1 (21 days)

Maintenance Dose:
- 200 billable units every 21 days

All other indications:
Loading Dose:
- 100 billable units days 1, 8, 15 of Cycle 1 (28 days)

Maintenance Dose:
- 100 billable units every 21 days for 8 cycles; then every 2 months for 2 years

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

1. Gazyva [package insert]. South San Francisco, CA; Genentech, Inc; March 2020. Accessed July 2021.

2. Referenced with permission from the NCCN Drugs and Biologics Compendium (NCCN Compendium®) obinutuzumab. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed July 2021.
3. Goede V, Fischer K, Busch R, et al. Chemoimmunotherapy with GA101 plus chlorambucil in patients with chronic lymphocytic leukemia and comorbidity: results of the CLL11 (BO21004) safety run-in. Leukemia. 2013 Apr; 27(5):1172-4. doi: 10.1038/leu.2012.252. Epub 2012 Aug 31.
4. 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.
5. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab- Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018 36:22, 2259-2266.
6. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med 2017; 377:1331.
7. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol. 2019;6(8):e429-e437. doi:10.1016/S2352-3026(19)30089-4.
8. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019;380(23):2225-2236. doi:10.1056/NEJMoa1815281.
9. Sharman JP, et al. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL) [abstract]. Blood 2019;134:Abstract 31.
10. 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):7523-7523.
11. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood. 2016;127(1):79-86. doi:10.1182/blood-2015-03-634394.
12. 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. 2014:2196-2202.
13. Sehn LH, Goy A, Offner FC, et al. Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study. J Clin Oncol. 2015;33(30):3467-3474. doi:10.1200/JCO.2014.59.2139.
14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 4.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed July 2021.
15. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas Version 4.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed July 2021.
16. Lexicomp Online. (2021, February). AHFS DI. *Obinutuzumab*. Retrieved September 16, 2021 from Lexicomp Online with AHFS.
17. MICROMEDEX Healthcare Series. Drugdex Evaluations. (2021, May). *Obinutuzumab*. Retrieved September 16, 2021 from MICROMEDEX Healthcare Series.

EFFECTIVE DATE

BlueCross BlueShield of Tennessee

Policy

Medical Policy Manual

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