Clinical Policy Title:	obinutuzumab
Policy Number:	RxA.385
Drug(s) Applied:	Gazyva®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Obinutuzumab is a CD20-directed cytolytic antibody. Obinutuzumab is indicated:

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
obinutuzumab (Gazyva®)	CLL/SLL	100 mg intravenously on day 1, 900 mg intravenously on day 2 of cycle 1, then 1000 mg intravenously on days 8 and 15 of cycle 1; begin the next cycle of therapy on day 29. For cycles 2 to 6, give obinutuzumab 1000 mg intravenously on day 1 repeated every 28 days. Administer obinutuzumab in combination with chlorambucil (0.5 mg/kg/day orally on day 1 and 15) in cycles 1 to 6.	See regimen
	FL	For patients with relapsed or refractory FL: 1000 mg intravenously on day 1, 8 and 15 of cycle 1, 1000 mg on day 1 of cycles 2-6 or cycles 2-8, and then 1000 mg every 2 months for up to 2 years. Administer in combination with bendamustine in six 28-day cycles. Patients who achieve stable disease, complete response or partial response to	See regimen

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		the initial 6 cycles should continue on 1000 mg as monotherapy for up to two years. For patients with previously untreated FL: administer obinutuzumab with one of the following chemotherapy regimens: 1) Six 28-day cycles in combination with bendamustine 2) Six 21-day cycles in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), followed by 2 additional 21-day cycles of obinutuzumab alone 3) Eight 21-day cycles in combination with CVP (cyclophosphamide, vincristine, prednisone) Patients with previously untreated FL who achieve a complete or partial response to the initial 6 or 8 cycles should continue on obinutuzumab 1000 mg as monotherapy for up to 2 years.	

Dosage Forms

- Single-dose vial: 1,000 mg/40 mL (25 mg/mL)

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (must meet all)**:**

1. Diagnosis of CLL or SLL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥18 years;
4. Request meets one of the following (a or b):*
   a. After initial loading doses, dose does not exceed 1,000 mg per 28-day cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   *Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration
Commercial: 6 months
Medicaid: 6 months

B. Follicular and other B-Cell Lymphomas (must meet all):
1. Diagnosis of one of the following B-cell lymphoma subtypes (a or b):
   a. Follicular lymphoma (grade 1-2);
   b. Other B-cell lymphomas (off-label):
      i. Marginal zone lymphoma (a, b, or c):
         a) Splenic marginal zone lymphoma;
         b) Nodal marginal zone lymphoma;
         c) Extranodal marginal zone lymphoma (1 or 2):
            1) Gastric mucosa-associated lymphoid tissue lymphoma;
            2) Non-gastric mucosa-associated lymphoid tissue lymphoma;
      ii. Histologic transformation of nodal marginal zone lymphoma to diffuse large B-cell lymphoma;
      iii. Diffuse large B-cell lymphoma;
      iv. High-grade B-cell lymphoma;
      v. Mantle cell lymphoma;
      vi. Castleman's disease;
      vii. Post-transplant lymphoproliferative disorders;
      viii. AIDS-related B-cell lymphoma;
      ix. Burkitt lymphoma;
2. If not FL, one of the following uses (a or b):
   a. Used as a substitute* for rituximab in patients experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens- Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis;
   *Re-challenge with the same anti-CD20 monoclonal antibody is not recommended and it is unclear if the use of an alternative anti-CD20 monoclonal antibody poses the same risk of recurrence.
   b. If marginal zone lymphoma (i or ii):
      i. Maintenance therapy if disease is rituximab-refractory, recurrent and has been treated with obinutuzumab and bendamustine;
      ii. Second-line or subsequent therapy in combination with bendamustine (see Appendix B for examples of prior therapy);
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age ≥ 18 years;
5. Request meets one of the following (a or b):**
   a. After initial loading doses, dose does not exceed 1,000 mg per 28-day cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   **Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is currently receiving obinutuzumab for a covered indication and has received this medication for at least 30 days;
3. Member is responding positively to therapy;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. After initial loading doses, new dose does not exceed 1,000 mg per 28-day cycle;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CLL: Chronic Lymphocytic Leukemia
FDA: Food and Drug Administration
FL: Follicular Lymphoma
MALT: Mucosa-Associated Lymphoid Tissue
NCCN: National Comprehensive Cancer Network
NHL: Non-Hodgkin Lymphoma
SLL: Small Lymphocytic Lymphoma

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
CLL/SLL Examples of first-line, second-line and subsequent therapies: • ibrutinib • acalabrutinib ± obinutuzumab • venetoclax + obinutuzumab • chlorambucil + obinutuzumab • high-dose methylprednisolone + rituximab • ibrutinib + obinutuzumab • chlorambucil • rituximab	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Marginal Zone Lymphomas Examples of first-line, second-line and subsequent therapies: • bendamustine + rituximab • RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) • RCVP (rituximab, cyclophosphamide, vincristine, prednisone) • Single-agent examples: rituximab; Leukeran® (chlorambucil) ± rituximab; cyclophosphamide ± rituximab; Imbruvica® (ibrutinib); Revlimid® (lenalidomide) ± rituximab; Copiktra® (duvelisib); Aliqopa® (copanlisib)	Varies	Varies

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

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

- Boxed warning(s):
  - Hepatitis B virus reactivation and progressive multifocal leukoencephalopathy

APPENDIX D: General Information

- Gazyva® can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception.
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as Gazyva®. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

References

1. Gazyva® Prescribing Information. South San Francisco, CA: Genentech, Inc.; January 2021. Available at: https://www.Gazyva®.com/. Accessed May 31, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed May 31, 2021.
3. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Version 4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed May 31, 2021.
4. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 31, 2021.
5. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed May 31, 2021.
6. Obinutuzumab, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed May 31, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy updated. 1. Formatting updated. 2. Policy updated. 3. Continued criteria for approval updated. 4. Approval duration updated. 5. Reference updated.	07/23/2020	09/14/2020
Policy was reviewed. 1. Dosing Information dosing regimen was updated from " chlorambucil (0.5 mg/kg…" to" chlorambucil (0.5 mg/kg/day…". 2. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. **3.** Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 4. Appendix B verbiage was updated to *"Below are suggested therapeutic alternatives.."* 5. Appendix B footnote was updated to," Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 6. Appendix D: General Information was established and updated to include " Gazyva® can cause fetal harm. Advise females of…". **7.** References were reviewed and updated.	05/31/2021	09/14/2021