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Idaho and select counties of Washington

**Medication Policy Manual**

**Policy No:** dru327

**Topic:** Gazyva®, obinutuzumab

**Date of Origin:** January 17, 2014

**Committee Review Date:** January 13, 2017

**Next Review Date:** January 2018

**Effective Date:** February 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Obinutuzumab (Gazyva) is an intravenously infused humanized monoclonal antibody that is administered with chlorambucil in the first-line treatment of chronic lymphocytic leukemia (CLL). It may also be used for relapsed or refractory follicular lymphoma (FL) when administered with bendamustine. Both CLL and FL are cancers associated with abnormal proliferation of B-cells. Obinutuzumab (Gazyva) attaches to the CD20 antigen on the surface of the B-cells, which leads to cell lysis (cell death).



## Policy/Criteria

- I. Most contracts require prior authorization approval of obinutuzumab (Gazyva) prior to coverage. Obinutuzumab (Gazyva) may be considered medically necessary when criterion A or B below is met.
  - A. Diagnosis of **chronic lymphocytic leukemia (CLL)** when criteria 1 and 2 below are met:
    1. Obinutuzumab (Gazyva) will be administered in combination with chlorambucil.

**AND**

    2. The patient has had no prior medication therapy for CLL.
  - OR**
  - B. Diagnosis of **relapsed or refractory follicular lymphoma (FL)** when criteria 1 and 2 below are met:
    1. There has been progression of disease on or after a rituximab-containing regimen.

**AND**

    2. Obinutuzumab (Gazyva) will be administered in combination with bendamustine for six cycles, followed by obinutuzumab (Gazyva) monotherapy.
- II. Administration, Quantity Limitations, and Authorization Period
  - A. Regence Pharmacy Services does not consider obinutuzumab (Gazyva) to be a self-administered medication.
  - B. When prior authorization is approved, obinutuzumab (Gazyva) may be authorized as follows:
    1. **CLL:** A single treatment course of up to eight 1,000-mg infusions in a 12-month period.
    2. **FL:** Up to eight 1,000-mg infusions in the initial 6-month period with bendamustine.
  - C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
    1. **CLL:** No additional treatment courses will be authorized.
    2. **FL:** Up to six 1,000-mg infusions in a 12-month period for a lifetime maximum of 2 years on obinutuzumab (Gazyva) monotherapy.
- III. Obinutuzumab (Gazyva) is considered investigational when used for all other conditions.

## Position Statement

- Obinutuzumab (Gazyva), an anti-CD20 humanized monoclonal antibody, is a B-cell-directed immunotherapy used in combination with chlorambucil for the treatment of chronic lymphocytic leukemia (CLL) or in combination with bendamustine for the treatment of relapsed or refractory follicular lymphoma (FL)
- Obinutuzumab (Gazyva) was studied in patients who had no previous therapy for their CLL, and who were not candidates for more aggressive chemotherapy due to advanced age and/or comorbid conditions.
- FDA approval was based on improved progression-free survival (PFS) in patients who received chlorambucil plus obinutuzumab (Gazyva) versus those who received chlorambucil alone. There is currently no mature overall survival data available.
- A treatment course of obinutuzumab (Gazyva) for CLL consists of three 1,000 mg intravenous infusions in the first cycle (28 days), followed by one 1,000 mg intravenous infusion per cycle (28 days) for five consecutive cycles. The first dose is divided over two days to monitor for severe infusion reactions. The safety and effectiveness of additional treatment courses has not been studied.
- Obinutuzumab (Gazyva) was also studied in patients with FL who had no response to, or progressed on a rituximab-containing regimen.
- FDA approval for FL was based on PFS in patients who received bendamustine plus obinutuzumab (Gazyva) versus bendamustine alone. There is currently no mature overall survival data available, nor is there any evidence that it improves any clinically relevant outcome such as symptom control or improved quality of life.
- A treatment course of obinutuzumab (Gazyva) for FL consists of 1,000 mg intravenous infusions on Days 1, 8, and 15 of Cycle 1 (28 days), then on Day 1 of Cycles 2-6 (28 days). After Cycle 6, obinutuzumab (Gazyva) should be given as monotherapy every 2 months for up to 2 years.
- There is a high potential for off-label use of obinutuzumab (Gazyva) in B-cell-mediated diseases other than CLL and FL; however, there is no evidence supporting its efficacy in these settings.
- Obinutuzumab (Gazyva), as well as all anti-CD20 monoclonal antibodies, carries a boxed warning describing a risk for hepatitis B virus reactivation and for progressive multifocal leukoencephalopathy (PML).
- Infusion reactions are common and may be severe. Premedication is recommended. The first dose should be administered slowly and divided over two days.
- Other common adverse effects include bone marrow suppression, fever, cough, and musculoskeletal disorder.

### *Clinical Efficacy*

- There is a single, low-quality, unpublished, open-label, randomized controlled trial evaluating obinutuzumab (Gazyva) in combination with chlorambucil as a first-line therapy for certain patients with chronic lymphocytic leukemia (CLL). <sup>[1,2]</sup>
  - \* Patients enrolled in the trial had confirmed B-cell CLL, had no prior medication treatment for their disease, and were not candidates for more aggressive chemotherapy due to comorbid conditions (e.g. reduced renal function). <sup>[1,2]</sup>
  - \* The primary endpoint in the study was investigator-reported progression-free survival (PFS). <sup>[1,2]</sup> Overall survival (OS) will be reported as a secondary endpoint. PFS has not been validated as an accurate predictor of OS in this setting. <sup>[3]</sup>
  - \* The study was completed in two stages. Stage 1 of the trial compared chlorambucil plus obinutuzumab (Gazyva) with chlorambucil alone. Stage 2 of the trial compared chlorambucil plus obinutuzumab (Gazyva) with chlorambucil plus rituximab (Rituxan). <sup>[1,2]</sup>
  - \* The obinutuzumab (Gazyva) treatment arm was reported to have a 12-month PFS advantage over chlorambucil alone (23 months and 11 months, respectively). <sup>[1,2]</sup>
  - \* In stage 2 of the trial, the obinutuzumab (Gazyva) treatment arm was reported to have an 11.5 month PFS advantage over the rituximab (Rituxan) treatment arm (26.7 months and 15.2 months, respectively). <sup>[4,5]</sup> OS data from this trial is not mature at this time.
  - \* Evidence from the trial was appraised as being of low quality due to the open-label design of the study and the high rate of attrition.
- There is a single, low-quality, unpublished, open-label, randomized controlled trial evaluating obinutuzumab (Gazyva) in combination with bendamustine as a therapy for certain patients with relapsed or refractory follicular lymphoma (FL) who had no response or progressed on a rituximab-containing regimen. <sup>[1]</sup>
  - \* Patients were randomized to receive either obinutuzumab (Gazyva) plus bendamustine or bendamustine alone. Patients who received obinutuzumab (Gazyva) plus bendamustine and did not have disease progression at the end of 6 months continued receiving obinutuzumab (Gazyva) monotherapy for 2 years.
  - \* The median PFS of the obinutuzumab (Gazyva) plus bendamustine arm has not been reached, although it is estimated to be 29.2 months. The reported median PFS of the bendamustine alone arm is 13.8 months.
  - \* The median overall survival has not been reached in either arm after about 45 months.
- Obinutuzumab (Gazyva) has not been studied in the relapsed or refractory CLL setting, first-line FL setting, or when used as a single agent for CLL. It has also not been evaluated in other B-cell mediated conditions (e.g. other non-Hodgkin's lymphomas).

- The National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guideline lists obinutuzumab (Gazyva) plus chlorambucil as a category 1, first-line therapy option for patients with CLL without del(17p)/TP53 mutations. The combination is listed as a category 3 recommendation in CLL with a del(17p)/TP53 mutation. In the relapsed or refractory setting, obinutuzumab (Gazyva) is listed as category 2A recommendation when given as monotherapy. [6]
- The NCCN B-cell Lymphomas guideline lists obinutuzumab (Gazyva) plus bendamustine as a category 2A recommendation for second-line therapy of grade 1-2 FL. [7]

**Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.**

### *Safety*

- Package labeling for obinutuzumab (Gazyva) carries a boxed warning for reactivation of hepatitis B virus and for progressive multifocal leukoencephalopathy (PML). [1]
- Infusion reactions are common and may be severe or fatal. Premedication with glucocorticoids, acetaminophen, and diphenhydramine is recommended prior to each infusion. The first infusion should be split over two days, with 100 mg infused on day 1 and 900 mg infused on day 2. [1]
- Obinutuzumab (Gazyva) should only be administered by a healthcare professional (HCP) with access to appropriate medical support (e.g. crash cart). [1]
- Common adverse effects (incidence  $\geq$  10%) include: infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders. [1]
- Live virus vaccines should not be administered prior to or during therapy with obinutuzumab (Gazyva). [1]

### *Dosing*

- Obinutuzumab (Gazyva) should only be given intravenously through a dedicated line by a healthcare professional (HCP). [1]
- A treatment course of obinutuzumab (Gazyva) is as follows (given in 28-day cycles) for CLL: [1]
  - \* 100 mg IV on day of 1 cycle 1, then 900 mg IV on day 2 of cycle 1
  - \* 1,000 mg IV on days 8 and 15 of cycle 1
  - \* 1,000 mg IV on day 1 of cycles 2 through 6
- A treatment course of obinutuzumab (Gazyva) is as follows (given in 28-day cycles) for FL: [1]
  - \* 1,000 mg IV on days 1, 8 and 15 of cycle 1
  - \* 1,000 mg IV on day 1 of cycles 2 through 6
  - \* 1,000 mg IV monotherapy every 2 months for 2 years

- The use of obinutuzumab (Gazyva) beyond one treatment course for CLL has not been studied.

<b>Cross References</b>
Arzerra®, ofatumumab, Medication Policy Manual, Policy No. 196
Imbruvica®, ibrutinib, Medication Policy Manual, Policy No. 326
Rituxan®, rituximab, Medication Policy Manual, Policy No. 214
Venclexta™, venetoclax, Medication Policy Manual, Policy No. 462
Zydelig®, idelalisib, Medication Policy Manual, Policy No. 363

<b>Codes</b>	<b>Number</b>	<b>Description</b>
HCPCS	J9999	Injection, obinutuzumab, 10 mg
ICD-10	C91.10	Chronic lymphoid leukemia without mention of having achieved remission
ICD-10	C82.9	Follicular lymphoma, unspecified

## References

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2. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Medical Review BLA 125-486; Obinutuzumab (Gazyva™). [cited 12/3/2013]; Available from: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2013/125486Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125486Orig1s000MedR.pdf)
3. Terasawa, T, Trikalinos, NA, Djulbegovic, B, Trikalinos, TA. Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: a multiple-treatment meta-analysis. *Cancer treatment reviews*. 2013 Jun;39(4):340-9. PMID: 22703832
4. Goede V, Fischer K, Busch R KC, et al. 6 Head-To-Head Comparison Of Obinutuzumab (GA101) Plus Chlorambucil (Clb) Versus Rituximab Plus Clb In Patients With Chronic Lymphocytic Leukemia (CLL) and Co-Existing Medical Conditions (Comorbidities): Final Stage 2 Results Of The CLL11 Trial. Abstract 60276; Presented at the December 2013 American Society of Hematology (ASH) Annual Meeting and Exposition, December 7-10, 2013, New Orleans, LA.
5. Goede, V, Fischer, K, Busch, R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *The New England journal of medicine*. 2014 Mar 20;370(12):1101-10. PMID: 24401022
6. NCCN Clinical Practice Guidelines in Oncology™. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v.1.2017. [cited 12/22/2016]; Available from: [www.nccn.org/professionals/physician\\_gls/pdf/cll.pdf](http://www.nccn.org/professionals/physician_gls/pdf/cll.pdf)
7. NCCN Clinical Practice Guidelines in Oncology™. B-cell Lymphomas v.1.2017. [cited 12/22/2016]; Available from: [www.nccn.org/professionals/physician\\_gls/pdf/b-cell.pdf](http://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf)

*Revision History*

<b>Revision Date</b>	<b>Revision Summary</b>
1/13/2017	Added coverage criteria for refractory or relapsing follicular lymphoma.
1/8/2016	Adjusted quantity limit to better reflect dosing in package labeling (limit to eight 1000-mg infusions as per package labeling).