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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 1, 2014
Subject:	Gazyva	**Page:**	1 of 7

Last Review Date: March 12, 2021

Gazyva

Description

Gazyva (obinutuzumab)

Background
Gazyva (obinutuzumab) is a monoclonal antibody intended to be used for treatment of patients with chronic lymphocytic leukemia (CLL), follicular lymphoma, gastric or nongastric MALT lymphoma, splenic marginal zone lymphoma, or nodal marginal zone lymphoma. Gazyva works by helping certain cells in the immune system attack cancer cells. In particular, Gazyva targets the CD20 antigen expressed on the surface of the pre B- and mature B-lymphocytes (1-3).

Regulatory Status
FDA-approved indication: Gazyva is a CD20-directed cytolytic antibody and is indicated: (1)

1. In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia
2. In combination with bendamustine followed by Gazyva monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
3. In combination with chemotherapy followed by Gazyva 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.

Off-Label Uses: (2-4)

1. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
    a. First-line therapy in patients without del(17p)/TP53
    b. First-line therapy in patients with del(17p)/TP53

   c. First-line therapy when used with Calquence (acalabrutinib)
   d. Patients unable to tolerate purine analogs as a single agent or in combination with chlorambucil
   e. Patients with relapsed or refractory disease as a single agent
2. Gastric MALT lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen and in combination with bendamustine
3. Nongastric MALT lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen and in combination with bendamustine
4. Splenic marginal zone lymphoma in patients who relapsed after, or are refractory to, a rituximab-containing regimen and in combination with bendamustine
5. Nodal Marginal Zone Lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen and in combination with bendamustine

Gazyva carries a boxed warning regarding hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML). Patients must be screened for HBV infection before treatment initiation. Positive patients must be monitored during and after Gazyva treatment. In the event of HBV reactivation, discontinue Gazyva and concomitant medications (1). Patients presenting with new onset or changes to pre-existing neurologic manifestations should be evaluated for the diagnosis of PML. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Gazyva therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML (1).

Gazyva can cause severe and life-threatening infusion reactions. Patients should be premedicated with acetaminophen, antihistamine and a glucocorticoid and closely monitored during the entire infusion (1).

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from Tumor Lysis Syndrome (TLS) can occur within 12-24 hours after the first infusion. Patients with high tumor burden and/or high circulating lymphocyte count (> 25 x 10^9/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol) and hydration beginning 12-24 hours prior to the infusion of Gazyva. For treatment of TLS, correct electrolyte abnormalities, monitor renal function, and fluid balance, and administer supportive care, including dialysis as indicated (1).

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following Gazyva therapy. Do not administer Gazyva to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection (1).

Gazyva has been shown to cause life threatening neutropenia and thrombocytopenia. Patients must be continuously monitored for infection, thrombocytopenia, and hemorrhagic events. In patients with Grade 3 or 4 neutropenia, consider administration of granulocyte colony-stimulating factors (G-CSF) and/or dose delays of Gazyva. Patients with severe and long lasting (>1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered as well. In patients with Grade 3 or 4 thrombocytopenia, platelet counts should be monitored frequently. Management of hemorrhage may require blood product support (1).

The safety and efficacy of immunization with live or attenuated viral vaccines during or following Gazyva therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery (1).

The safety and effectiveness of Gazyva in patients less than 18 years of age have not been established (1).

Related policies
Arzerra, Bendeka, Imbruvica, Rituximab, Treanda, Zydelig

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Gazyva may be considered **medically necessary** in patients that are 18 years of age and older with CD20-positive chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL), follicular lymphoma (FL), gastric or nongastric MALT lymphoma, splenic marginal zone lymphoma, or nodal marginal zone lymphoma and if the conditions indicated below are met.

Gazyva may be considered **investigational** in patients less than 18 years of age and for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. CD20-positive chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL)

   AND ONE of the following:
   a. First-line therapy in patients without del(17p)/TP53
   b. First-line therapy in patients with del(17p)/TP53
   c. First-line therapy when used in combination with acalabrutinib
   d. Inadequate response or intolerance to purine analog
   e. Relapsed or refractory disease as a single agent

2. Follicular lymphoma (FL)

   AND ONE of the following:
   a. Stage II bulky, III or IV
      i. Used in combination with chemotherapy during the initial 6 cycles of treatment followed by use as monotherapy
   b. Patient is relapsed or refractory to a rituximab-containing regimen
      i. Used in combination with bendamustine during the initial 6 cycles of treatment followed by use as monotherapy

3. Gastric or Nongastric MALT lymphoma
   a. Patient is relapsed or refractory to a rituximab-containing regimen
   b. Used in combination with bendamustine during the initial 6 cycles of treatment followed by use as monotherapy

4. Splenic Marginal Zone lymphoma
   a. Patient is relapsed or refractory to a rituximab-containing regimen
   b. Used in combination with bendamustine during the initial 6 cycles of treatment followed by use as monotherapy

5. Nodal Marginal Zone Lymphoma
   a. Patient is relapsed or refractory to a rituximab-containing regimen
   b. Used in combination with bendamustine during the initial 6 cycles of treatment followed by use as monotherapy

AND ALL of the following:
1. Absence of active infection
2. Patient has or will be screened for hepatitis B prior to initiation of therapy and

will be continued to be monitored during treatment if positive
3. Patient will be monitored for signs and symptoms of progressive multifocal leukoencephalopathy (PML)

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. CD20-positive chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL)
2. Follicular lymphoma (FL)
3. Gastric or Nongastric MALT lymphoma
4. Splenic Marginal Zone lymphoma
5. Nodal Marginal Zone Lymphoma

AND ALL of the following:
1. **NO** disease progression or unacceptable toxicity
2. Absence of active infection
3. Patient will be monitored for signs and symptoms of progressive multifocal leukoencephalopathy (PML)

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Duration 24 months

Rationale

Summary
Gazyva (obinutuzumab) is a monoclonal antibody intended to be used for treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL), follicular lymphoma, gastric or nongastric MALT lymphoma, splenic marginal zone lymphoma, or nodal marginal zone lymphoma. Gazyva carries a boxed warning regarding hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML). Gazyva can cause severe and life-threatening infusion reactions. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following Gazyva therapy. Do not administer Gazyva to patients with an active infection. Gazyva has been shown to cause life-threatening neutropenia and thrombocytopenia. The safety and efficacy of immunization with live or attenuated viral vaccines during or following Gazyva therapy has not been studied. The safety and efficacy of Gazyva in patients less than 18 years of age have not been established (1-3).

Prior approval is required to ensure the safe, clinically appropriate and cost-effective use of Gazyva while maintaining optimal therapeutic outcomes.

References

1. Gazyva [package insert]. South San Francisco, CA: Genentech, Inc.; March 2020.
2. NCCN Drugs & Biologics Compendium® 2021. National Comprehensive Cancer Network, Inc.
3. NCCN Clinical Practice Guidelines in Oncology® Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (Version 2.2021). National Comprehensive Cancer Network, Inc. December 2020.
4. NCCN Clinical Practice Guidelines in Oncology® B-cell Lymphomas (Version 1.2021). National Comprehensive Cancer Network, Inc. January 2021.

Policy History

Date	Action
November 2013	Addition to PA
March 2014	Annual review
December 2014	Annual editorial review and reference update

December 2015	Annual review and reference update
March 2016	Addition of chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) with one of the following: first-line therapy in patients without del(11)q or del(17p)/TP53, first-line therapy in patients with del(11)q or del(17p)/TP53 when used in combination with chlorambucil, inadequate response or intolerance to purine analog, or relapsed or refractory disease; with follicular lymphoma (FL) when the patient is relapsed or refractory to a rituximab-containing regimen and used in combination with bendamustine during the initial 6 cycles of treatment followed by use as monotherapy; with gastric or nongastric MALT lymphoma that is relapsed or refractory to a rituximab-containing regimen; splenic marginal zone lymphoma that is relapsed or refractory to a rituximab-containing regimen. Policy number change from 5.04.29 to 5.21.29
September 2016	Annual review
June 2017	Annual editorial review and reference update Addition of age limit to renewal criteria
December 2017	Addition of Follicular lymphoma stage II bulky, III or IV used in combination with chemotherapy during the initial 6 cycles of treatment followed by use as monotherapy. Addition of nodal marginal zone lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen and in combination with bendamustine Addition of in combination with bendamustine for gastric or nongastric MALT lymphoma and splenic marginal zone lymphoma
March 2018	Annual review
June 2019	Annual review and reference update
March 2020	Annual review and reference update. Revised NCCN indications for CLL and SLL
June 2020	Annual review and reference update
March 2021	Annual editorial review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.