

Obinutuzumab (Gazyva®)**Criteria for Use****April 2016**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive obinutuzumab.*

- Care not provided by a VA or VA purchased care (e.g. Choice Program, Fee Basis) hematology/oncology provider.
- Active infection (bacterial, viral or fungal) requiring systemic therapy. See Issues for Consideration.
- AST, ALT > 5x ULN for > 2 weeks and/or bilirubin > 3x ULN unless due to underlying disease or moderate-severe hepatic impairment (Child-Pugh B or C). (see Issues for Consideration)
- Patient has not been screened for Hepatitis B Virus (HBV). See Issues for Consideration.
- Planning to receive live virus vaccine during therapy. See Issues for Consideration.
- Creatinine clearance < 30 ml/min, as drug has not been studied in this population
- Absolute Neutrophil Count (ANC) $\leq 1.5 \times 10^9$ /L unless cytopenia is caused by underlying disease
- Platelet count $\leq 75 \times 10^9$ /L unless cytopenia is caused by underlying disease

Inclusion Criteria *The following must be fulfilled in order to meet criteria.*

- Diagnosis of CD20+ Chronic Lymphocytic Leukemia (CLL)
 - AND has not received prior treatment for CLL
 - AND is not a candidate for fludarabine-based therapy due to existing comorbidities or renal insufficiency
 - AND is a candidate for concomitant chlorambucil therapy

OR

- Diagnosis of CD20+ Follicular Lymphoma (FL). See Issues for Consideration.
 - WITH disease that is REFRACTORY to rituximab
 - Defined as disease that is unresponsive to rituximab as monotherapy or in combination with chemotherapy OR
 - Disease that has progressed within 6 months of completion of the last dose of a rituximab-containing regimen
 - AND patient is a candidate for concomitant bendamustine therapy (e.g. able to tolerate myelosuppressive therapy, etc.)

AND

- Goals of care and role of palliative care consult have been discussed and documented.
- ECOG* Performance Status 0 - 2

For women of childbearing potential

- Pregnancy should be excluded prior to receiving obinutuzumab and the patient provided contraceptive counseling on potential risk vs. benefit of taking obinutuzumab if patient were to become pregnant.

Dosage and Administration

- Dosing for CLL, Cycle #1: obinutuzumab 100 mg IV on day 1 and 900 mg IV on day 2, 1000 mg IV on days 8 and 15
 - Cycles #2-6: obinutuzumab 1000 mg IV on day 1
- Dosing for FL, Cycle #1: obinutuzumab 1000 mg on days 1, 8 and 15
 - Cycles #2-6: obinutuzumab 1000 mg IV on day 1
 - Maintenance: obinutuzumab 1000 mg IV every 2 months for 2 years
- Infusion Related Reactions (IRR) prophylaxis. Premedication prior to each obinutuzumab infusion includes acetaminophen, antihistamine and glucocorticoid. Refer to prescribing information for specific recommendations.
- Hypotension risk. Consider withholding antihypertensive therapies for 12 hours prior to and throughout each obinutuzumab infusion, and the first hour after administration. For those at increased risk of hypertensive crisis, consider benefits versus risks of withholding antihypertensive

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meds.

- TLS risk. Initiate tumor lysis syndrome (TLS) prophylaxis (e.g. anti-hyperuricemics and adequate hydration) prior to start of therapy in patients with evidence of high tumor burden or renal impairment. Continue prophylaxis prior to each infusion, as needed.
- Antimicrobial prophylaxis. Consider antimicrobial (antiviral and antifungal) prophylaxis in patients with Grade 3 or 4 neutropenia that lasts more than one week. Continue until neutropenia resolves to Grade 1 or 2.
- HBV prophylaxis. (See Issues for Consideration)
- Treatment interruptions for toxicity. Consider interrupting therapy if an infection, Grade 3 or 4 cytopenia, or \geq Grade 2 non-hematologic toxicity
- Preparation and administration. Refer to prescribing information.

Monitoring

- Signs/symptoms of infusion-related reactions during obinutuzumab infusions, especially during administration of the first 1000 mg. IRR can occur with subsequent infusions as well. Reactions can occur within 24 hours of receiving obinutuzumab. Symptoms may include hypotension, tachycardia, dyspnea and respiratory symptoms. Most frequently reported include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia and chills.
- Patients with evidence of current or prior HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment.
- New onset neurologic changes or changes to preexisting neurologic conditions could indicate JC virus infection. Consider diagnosis of Progressive Multifocal Leukoencephalopathy (PML) in such cases.
- Laboratory parameters of patients at risk for TLS, which may include renal function, urine pH, fluid balance and electrolyte abnormalities.
- Signs/symptoms of bacterial, fungal and/or viral infections during and following therapy.
- Neutropenia and/or febrile neutropenia. Neutropenia can be late onset (occurring more than 28 days following completion of treatment) and/or prolonged (lasting longer than 28 days).
 - Consider dose delays in those with Grade 3 or 4 neutropenia and/or administration of granulocyte colony stimulating factors, as appropriate, based upon risk of febrile neutropenia and patient characteristics.
 - Those with severe neutropenia lasting > 1 week, should receive antimicrobial, antiviral and antifungal prophylaxis until neutropenia is resolved to Grade 1 or 2.
- Thrombocytopenia and hemorrhagic events. Monitor platelet count and signs of bleeding, especially during the first cycle.
 - Consider withholding concomitant medications that may increase bleed risk (anticoagulants, platelet inhibitors), especially during the first cycle
 - Monitor platelet count more frequently and consider obinutuzumab and chemotherapy delays or chemotherapy dose-reductions.
 - Platelet transfusions may be necessary.
- Liver function tests should be monitored during treatment, especially during the first cycle. Consider an interruption of therapy or discontinuation for hepatotoxicity.
- Evidence of disease response or progression (via radiographic scan or symptomatology). Assess disease signs and symptoms prior to each cycle of obinutuzumab with disease status evaluation every 2 months.

Issues for Consideration

- Obinutuzumab received FDA approval 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. This approval is based upon results from the GADOLIN trial, which is available in abstract form. The primary endpoint, PFS, was significantly improved in the combination arm. ORR and OS were not different. Grade ≥ 3 adverse events were more common in the combination arm, notably neutropenia and infusion-related reactions. Use should be adjudicated locally on a case-by-case basis.
- Obinutuzumab and chlorambucil have been shown to improve PFS in previously untreated CLL patients that are not candidates for fludarabine-based therapy. No significant difference has been noted with regard to OS.
- TLS Risk. Initiate tumor lysis syndrome (TLS) prophylaxis (e.g. anti-hyperuricemics and adequate hydration) prior to start of therapy in patients with evidence of high tumor burden
- HBV Reactivation. ASCO recommends that providers screen patients for HBV infection prior to starting anti-CD20 therapy. Screening should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). Antiviral therapy (e.g. entecavir or tenofovir) should be initiated before starting or contemporaneously with anti-CD20 therapy in patients HBsAg-positive OR anti-HBc-positive and continue for at least 12 months following therapy, as agreed upon by hepatitis and hematology providers. All patients should be screened for HIV prior to starting antiviral therapy.
- Live vaccines. Safety and efficacy of immunization with live or attenuated viral vaccines during or following therapy has not been evaluated. Live vaccine immunizations are not recommended during treatment and until B-cell recovery (i.e. at least 3 months following end of therapy)
- Infection risk. Serious bacterial, fungal and new or reactivated viral infections can occur during and following obinutuzumab therapy. Do not administer to patients with an active infection. Those with a history of recurring or chronic infections may be at increased risk of infection.

Discontinuation Recommendations

- Patient develops signs of anaphylaxis during the infusion
- Grade 4 IRR or recurrent Grade 3 IRR symptom upon re-challenge
- Non-compliance with therapy, laboratory or follow-up requests
- Decline in ECOG performance status to level unacceptable for patient to maintain quality of life
- Evidence of HBV reactivation. Resumption in those whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.
- Evidence of progressive disease

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